

Question 1 of 198

A 28-year-old female presents with a 4-day history of fevers and joint pain. She has recently returned from a 3 month gap year trip to the South-East Asia three days ago and reports no ill health during her travels. She has no past medical history, does not smoke, drinks minimal alcohol and denies the use of illicit drugs. During her travels, she reports two episodes of unprotected sexual contact with a non-regular partner. Although she knew she would be entering a malaria area and was indeed bitten by mosquitoes on a number of occasions, she did not take any malaria prophylaxis.

On examination, heart sounds and chest examination are both normal. A maculopapular rash is noted on her left thigh and right upper arm, with bilateral conjunctival injection. Abdominal examination reveals a soft abdomen with no masses. She has a significantly joint and muscle pains, limiting your neurological examination. She is alert and orientated to time and place, scoring 10/10 on abbreviated mental testing. Her blood tests are as follows:

Hb 109 g/l  
Platelets  $45 \times 10^9/l$   
WBC  $3.5 \times 10^9/l$

Na<sup>+</sup> 137 mmol/l  
K<sup>+</sup> 3.8 mmol/l  
Urea 7.1 mmol/l  
Creatinine 100  $\mu$ mol/l  
CRP 70 mg/l

Bilirubin 7  $\mu$ mol/l  
ALP 30 u/l  
ALT 162 u/l

Her first malaria film is negative and a chest radiograph is unremarkable.

What is the most likely diagnosis?

[Gonorrhoea with reactive arthritis16% HIV seroconversion14% Dengue fever58% Malaria falciparum6% Typhoid5%](#)

The context of this patient should alert you to that of fever in a returning traveller. This is a

patient who presents with a combination of fever, myalgia and arthralgia, skin rash, conjunctival injection, raised ALT, thrombocytopaenia and leucopenia, strongly suggestive of dengue fever. The key differential for a returning traveller from South East Asia, where ingestion of contaminated water is possible, is to consider is also typhoid fever, which also presents with a skin rash (classically a rose spot) with diarrhoea and vomiting much more prominent. Although she had unprotected sex during her travel, gonorrhoea presents more typically with a migratory arthritis and tenosynovitis with discharge. Leucopenia is classical of dengue fever and does not necessarily suggest immunodeficiency, possibly secondary to HIV.

## **Dengue fever**

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

### Basics

- transmitted by the *Aedes aegypti* mosquito
- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

### Features

- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

A 71-year-old gentleman presented to the emergency department with a headache, myalgia and fever. These symptoms all started one day ago. He has a past medical history of hypertension, ischaemic heart disease, type 2 diabetes, congestive cardiac failure and bilateral hip replacement. His medications include amlodipine, ramipril, aspirin, atorvastatin, gliclazide, calcium carbonate with colecalciferol (Adcal-D3) and paracetamol. He denies any allergies. He is concerned that he has influenza as he visited a friend in hospital last week who had been diagnosed with influenza A.

On examination, he appears sweaty and feels hot to touch. His chest is clear on auscultation. He is placed in a side room for observation and viral throat swabs are requested.

Observations:

Oxygen saturation 96% on room air

Respiratory rate 18/min

Blood pressure 129/93mmHg

Heart rate 77/min

Temperature 38.1°C

What is the most appropriate treatment?

[Supportive management only 17% Salbutamol 3% Zanamivir 11% Amantadine 4% Oseltamivir 65%](#)

The correct answer is oseltamivir. This is a patient presenting with symptoms of influenza following recent exposure. The first aspect to consider is if he needs any antiviral drugs. Since he presented within 48 hours of the onset of symptoms and is in an at-risk group because of his diabetes he would warrant antiviral treatment and therefore supportive management is not the most appropriate treatment. Salbutamol is not indicated for flu alone. Zanamivir is second line treatment for influenza, whilst amantadine is no longer recommended for use in the treatment of influenza.

## **Influenza**

### **Features**

The following are typically seen:

- fever greater than 38°C
- myalgia
- lethargy
- headache

- rhinitis
- sore throat
- cough
- diarrhoea and vomiting

## Management

Consider prescribing antiviral treatment for influenza if all of the following apply:

- 1) The patient is in an at-risk group\* or is felt to be at risk of developing a serious complication
- 2) There is circulating influenza nationally
- 3) The patient is able to start treatment within 48 hours from the onset of symptoms (36 hours for zanamivir)

Antivirals for influenza

- First line: oseltamivir
- Second line: zanamivir
- For immunocompromised adults and in renal impairment: zanamivir

\*Chronic disease of respiratory, cardiac, renal, hepatic or neurological nature, diabetes, immunosuppression or have morbid obesity.

Source:

'Influenza - Seasonal.' Clinical Knowledge Summaries. National Institute for Health and Care Excellence, Oct. 2015.

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A 28-year-old man attends clinic for his 6 monthly HIV check. He was diagnosed with HIV 4 years ago and has been stable on Eviplera (emtricitabine/rilpivirine/tenofovir). He was recently started on a new medication by his GP.

Blood results are as follows:

Hb	134 g/l	Na <sup>+</sup>	136 mmol/l
Platelets	345 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.2 mmol/l
CD4	580 * 10 <sup>9</sup> /l (normal range 500-1500)	Urea	6.5 mmol/l



Viral load 1480 copies/ml\* 10<sup>9</sup>/l

Creatinine 65 µmol/l

What new medication was started which would explain these results?

[Omeprazole 53% Ciclosporin 17% Tacrolimus 12% Celecoxib 9% Diclofenac 9%](#)

PPIs are contraindicated in patients on Eviplera (emtricitabine/rilpivirine/tenofovir). They reduce the absorption of rilpivirine which can cause viral blips, with subsequent virological failure and resistance

Concurrent use of tenofovir with ciclosporin, tacrolimus, celecoxib or diclofenac, can increase the risk of nephrotoxicity.

Proton pump inhibitors are absolutely contraindicated in patients on Eviplera (emtricitabine/rilpivirine/tenofovir). They reduce the absorption of rilpivirine which can cause viral blips, with subsequent virological failure and resistance.

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

### Question 4 of 198

A 36-year-old gentleman was admitted to the Medical Admission Unit. His principle complaint was watery diarrhoea which has been present for the last few weeks. He had not noticed the presence of blood or mucus in the stool. He also complained of transient pain on swallowing, and weight loss of 2 stones over the last year. He denied the presence of respiratory symptoms and abdominal pain. He had no past medical history of note from his GP records. He consumes 20 cans of standard strength lager per week, smokes 20 cigarettes per day and denies recreational drug use. He had no fixed abode.

On examination, he was unkempt and dishevelled, with a BMI of 17.1 kg/m<sup>2</sup>. Cardiovascular and respiratory examinations were unremarkable except for an oxygen saturation of 94% on room air. His heart rate was 92/min, blood pressure 112/62 mmHg and temperature 36.7°C. Abdominal examination was also unremarkable though examination of the oral cavity revealed the presence of multiple aphthous ulcers. Examination of the neck revealed multiple small palpable cervical lymph nodes. Fundoscopy revealed the presence of white patches but otherwise, nil else and central and peripheral nervous system examination was otherwise normal. Skin examination revealed multiple pearly pink umbilicated nodules.

Initial investigations revealed the following:

Hb        122 g/l

Platelets  $189 \times 10^9/l$

WBC  $3.6 \times 10^9/l$

Chest x-ray: normal appearances of the heart and chest

ECG: 92bpm normal sinus rhythm, no other abnormalities seen

Urinalysis: normal

Stool MCS: normal interim results, pending further analysis

Which is the single investigation most likely to lead to the underlying diagnosis?

[CT head, chest, abdomen and pelvis 6% Upper gastrointestinal endoscopy 9% Bone marrow biopsy 5% Colonoscopy 9% HIV serology 72%](#)

This gentleman has several conditions strongly suggestive of Acquired Immunodeficiency Syndrome (AIDS). He has features of cytomegalovirus (CMV) retinitis and oesophagitis caused by either CMV or other infections such as herpes simplex virus (HSV) and candidiasis. His loose stools are most likely representative of Cryptosporidium infection which would not be found on a conventional initial stool microscopy, culture and sensitivity test. He also has a skin infection in keeping with Molluscum contagiosum. Testing for HIV serology is, therefore, the best option.

### **HIV: seroconversion**

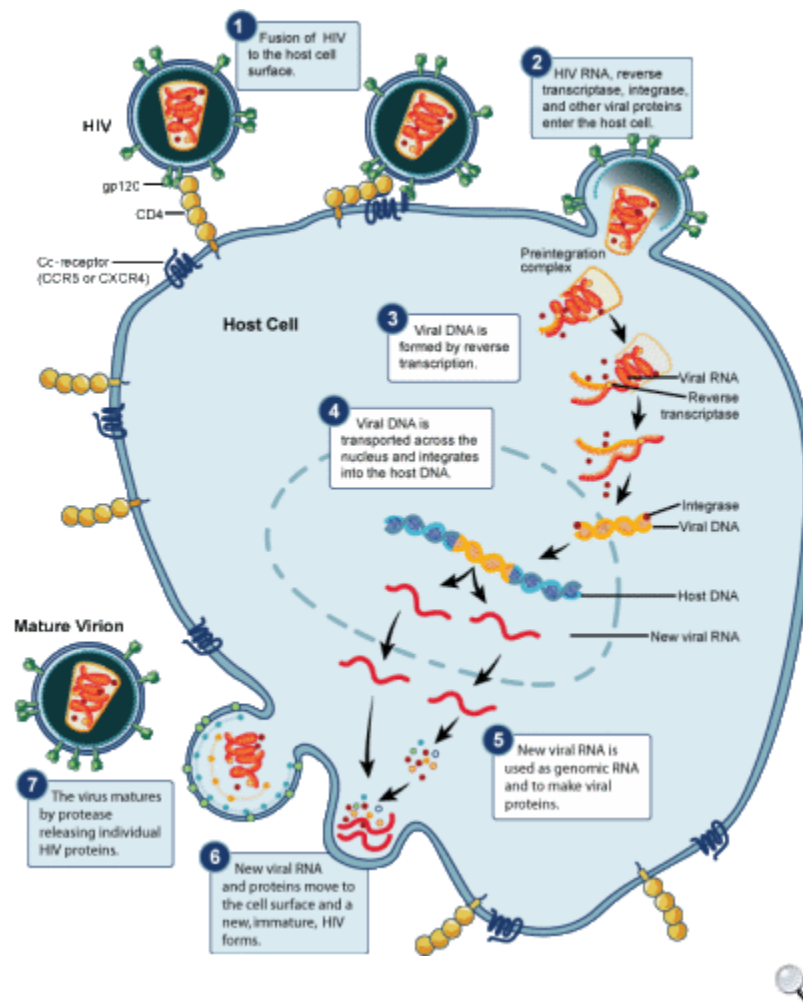
HIV seroconversion is symptomatic in 60-80% of patients and typically presents as a glandular fever type illness. Increased symptomatic severity is associated with poorer long term prognosis. It typically occurs 3-12 weeks after infection

#### **Features**

- sore throat
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea
- maculopapular rash
- mouth ulcers
- rarely meningoencephalitis

#### **Diagnosis**

- antibodies to HIV may not be present
- HIV PCR and p24 antigen tests can confirm diagnosis



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

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A 44-year-old woman with a background of asthma who has required frequent use of oral corticosteroids is inquiring about vaccinations available to her. Which one of the following should be recommended?

[23-valent unconjugated pneumococcal polysaccharide vaccine and influenza vaccine44%](#) [13-valent conjugated pneumococcal polysaccharide vaccine only5%](#) [23-valent unconjugated pneumococcal polysaccharide vaccine only7%](#) [13-valent conjugated pneumococcal polysaccharide vaccine and influenza vaccine27%](#) [Influenza vaccine only18%](#)

Patients with chronic respiratory conditions including asthma requiring frequent use of oral steroids should be offered both the 23-valent unconjugated pneumococcal polysaccharide vaccine and the influenza vaccine. In this population, the pneumococcal vaccine is usually given as a once off but may be required 5 yearly depending on the underlying condition and the age of the patient. The influenza vaccine, however, is given annually.

The 13-valent conjugated pneumococcal polysaccharide vaccine is routinely given to infants as it has been found to be more effective given their less mature immune systems.

## **Pneumococcal vaccine**

There are two type of pneumococcal vaccine currently in use:

- pneumococcal conjugate vaccine (PCV)
- pneumococcal polysaccharide vaccine (PPV)

The PCV is given to children as part of their routine immunisations (at 2, 4 and 13 months).

The PPV is offered to all adults over the age of 65 years, to patients with chronic conditions such as COPD and to those who have had a splenectomy (see below).

Groups who should be vaccinated:

- asplenia or splenic dysfunction
- chronic respiratory disease: COPD, bronchiectasis, cystic fibrosis, interstitial lung disease. Asthma is only included if 'it requires the use of oral steroids at a dose sufficient to act as a significant immunosuppressant'
- chronic heart disease: ischaemic heart disease if requiring medication or follow-up, heart failure, congenital heart disease. Controlled hypertension is not an indication for vaccination
- chronic kidney disease
- chronic liver disease: including cirrhosis and chronic hepatitis
- diabetes mellitus if requiring medication
- immunosuppression (either due to disease or treatment). This includes patients with any stage of HIV infection
- cochlear implants
- patients with cerebrospinal fluid leaks

Adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years.

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A 86-year-old male is admitted with a two day history of abdominal pain and diarrhoea. His past medical history includes gastro-oesophageal reflux disease which is treated with omeprazole.

Blood results are as follows:

Hb	135 g/l	Na <sup>+</sup>	138 mmol/l
Platelets	385 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.2 mmol/l
WBC	14.1 * 10 <sup>9</sup> /l	Urea	8.5 mmol/l
Neuts	12.2 * 10 <sup>9</sup> /l	Creatinine	110 µmol/l
Lymphs	1.1 * 10 <sup>9</sup> /l	CRP	66 mg/l

Stool cultures Positive for *Clostridium difficile* toxin

This is his second episode of *Clostridium difficile* infection in the past 4 weeks. You decide to treat with fidaxomicin 200mg twice daily for 10 days.

What other management option would you consider?

[Stop omeprazole53%](#)[Faecal transplant22%](#)[Probiotics15%](#)[Intravenous immunoglobulin \(IVIG\)4%](#)[Loperamide6%](#)

PPIs are a risk factor for *Clostridium difficile* infection

This is the patients second *Clostridium difficile* infection. Fidaxomicin is now the currently preferred agent for recurrence. Tapering followed by pulsed doses of vancomycin may be of value however there is concern for its use due to rising prevalence of vancomycin resistance Enterococci (VRE).

Medications used to slow or stop diarrhoea, such as loperamide may worsen *C. difficile* infection and are therefore not recommended.

With regards to probiotics, meta-analyses have failed to demonstrate statistically significant efficacy in treating or preventing *C.difficile*, and they are therefore not currently recommended.

Several case reports and small series have been published regarding the use of IVIG to treat refractory disease.

Faecal transplant has been demonstrated to be highly effective however it is utilised as a last line resort primarily because of practical and aesthetic concerns.

Proton pump inhibitors have been demonstrated as a risk factor for *C. difficile* infection. Therefore, the most appropriate option in this case would be to discontinue omeprazole.

## **Clostridium difficile**

*Clostridium difficile* is a Gram positive rod often encountered in hospital practice. In the UK it can be found in 3% of normal adults and up to 66% of babies. It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.

### **Risk factors**

- Broad spectrum antibiotics
- Use of PPI and H<sub>2</sub> receptor antagonists
- Contacted with persons infected with *C. difficile*

### **Features**

- Diarrhoea
- Abdominal pain
- A raised white blood cell count is characteristic
- If severe, toxic megacolon may develop

Diagnosis is made by detecting *Clostridium difficile* toxin (CDT) in the stool

### **Management**

- First-line therapy is oral metronidazole for 10-14 days
- If severe, or not responding to metronidazole, then oral vancomycin may be used
- Patients who do not respond to vancomycin may respond to oral fidaxomicin
- Patients with severe and unremitting colitis should be considered for colectomy

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The Medical Emergency Team (MET) is summoned to the Surgical Unit to assist with the management of an acutely unwell patient.

The patient is a 21-year-old male who underwent open surgery for perforated appendicitis 3 days ago. The Surgical Registrar informs you that faecal contamination of the abdomen was noted during the operation and that a peritoneal washout was performed.

24 hours later, the patient began to complain of worsening abdominal pain. He became febrile in the early hours of the morning and blood cultures were taken. Since then, he has become progressively more unwell. He was taken down for an urgent abdominal ultrasound mid-afternoon, but the nurses were so concerned about his condition when he arrived back on the ward that a MET call was put out.

On examination, the patient is responsive to voice. He is febrile at 38.9°C, his pulse is 131bpm and his blood pressure is 72/53mmHg. His peripheries are warm and clammy. Palpation of the abdomen reveals localised tenderness and guarding in the right iliac fossa. The surgical wound appears clean with minimal surrounding erythema.

As you prepare to place a large bore IV cannula the Surgical FY1 passes you some results that have recently been phoned through:

Abdominal ultrasound Anechoic fluid collection in the right iliac fossa

Blood culture                      Gram-positive cocci both bottles - further information to follow

Which of the following organisms is most likely to be isolated from the blood culture?

[Staphylococcus epidermidis15%](#)[Escherichia coli7%](#)[Streptococcus pyogenes10%](#)[Enterococcus faecalis53%](#)[Staphylococcus aureus15%](#)

Although on first glance this may appear to be a 'surgical case', it is important to remember that MET or 'crash' teams are called to attend a variety of patients, some of whom may be admitted under the care of other specialties. On-call medical doctors need to be able to apply their knowledge to a range of situations, particularly when they fall outwith the remit of their day-to-day practice.

A significant amount of surgical information is presented in this vignette, however, the underlying diagnosis is given to the candidate and the question is actually designed to test the candidate's knowledge of pathogenic bacteria and the illnesses they cause.

Strep. pyogenes is a common cause of pharyngitis and soft tissue infections, occasionally giving rise to septicaemia. It would be unlikely to cause illness in the case described above.

Staph. aureus and Staph. epidermidis are commensal organisms that commonly cause septicaemia in critically ill patients, often secondary to the colonisation of indwelling lines. This



vignette makes no mention of any such devices and we are told that the surgical wound is clean, making primary staphylococcal wound infection unlikely.

*Escherichia coli* is a gram-negative bacillus and is, therefore, inconsistent with the blood culture results described.

*Enterococcus faecalis* is a group D streptococcus. It is a gut commensal and a well-known cause of intra-abdominal infections. In the case described, it is likely that faecal contamination of the abdomen lead to the formation of an abscess and consequent *Enterococcus* bacteraemia.

## **Streptococci**

Streptococci are gram-positive cocci. They may be divided into alpha and beta haemolytic types

### **Alpha haemolytic streptococci (partial haemolysis)**

The most important alpha haemolytic *Streptococcus* is *Streptococcus pneumoniae* (pneumococcus). Pneumococcus is a common cause of pneumonia, meningitis and otitis media. Another clinical example is *Streptococcus viridans*

### **Beta haemolytic streptococci (complete haemolysis)**

These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

#### **Group A**

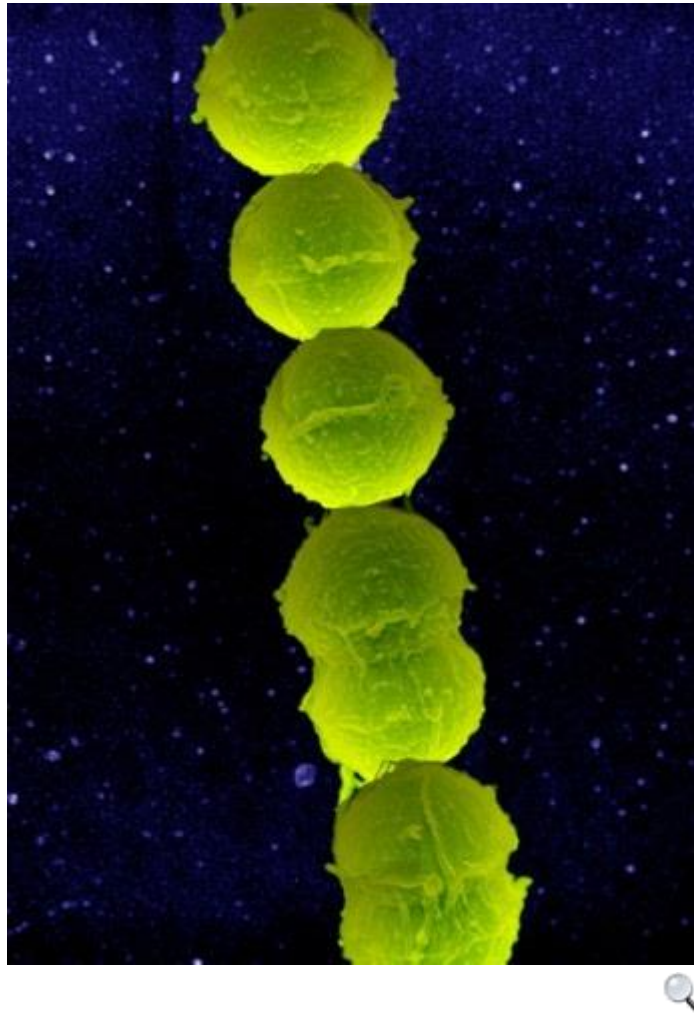
- most important organism is *Streptococcus pyogenes*
- responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis
- immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis
- erythrogenic toxins cause scarlet fever

#### **Group B**

- *Streptococcus agalactiae* may lead to neonatal meningitis and septicaemia

#### **Group D**

- *Enterococcus*



Group B streptococcus bacteria. Credit: NIAID

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A 25-year-old woman is started on antiretroviral therapy for HIV. She attends the GP 1 week later complaining of dizziness and nightmares. She is unable to work due to feeling muddled and disconnected. Which drug is responsible?

[Abacavir 11%](#) [Efavirenz 43%](#) [Lamivudine 16%](#) [Tenofovir 13%](#) [Zidovudine 18%](#)

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is frequently known to cause disturbing dreams and other cognitive disturbances in 50% of patients in the first month of

treatment.

The most concerning side effect of Abacavir is a hypersensitivity reaction that can lead to fever, malaise, nausea and skin rash which can be very severe. It is strongly associated with a specific allele at the human leukocyte antigen B locus, HLA-B\*57:01.

Lamivudine and Zidovudine are nucleoside analogue reverse transcriptase inhibitors (NRTIs). The NRTIs were the first class of antiretroviral drugs developed. As with all drugs in their class, they can cause a potentially fatal lactic acidosis & severe hepatomegaly with steatosis when used alone or in combination with other antiretrovirals.

Tenofovir is a nucleotide analogue reverse transcriptase inhibitors (NtRTI), it is a prodrug, the commonest side effects are gastrointestinal.

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

#### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

#### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

#### Question 9 of 198

A 43 year old man attends for follow up at the Infectious Diseases clinic. He is an HIV-positive patient who has been well while on treatment for the last 13 years. His current treatment regimen is emtricitabine, atazanavir and tenofovir. He has however begun to notice altered taste and a difficulty in swallowing over the last couple of months. In the last few days he has even noticed a white coating in his mouth that is not removed by vigorous scrubbing with his toothbrush. He describes being compliant with his medications and not taking any illicit drugs. He no longer has unprotected sexual intercourse. The only change that is identified is that he recently visited his GP with non-specific symptoms and was started on a new medication.

CD4 count in clinic 4 months ago 526

CD4 count currently 210

What medication is the GP likely to have started?

[Lansoprazole51%Aspirin5%Amitriptyline20%Paracetamol4%Simvastatin20%](#)

Interactions between anti-retroviral drugs and other more common medications are many and varied. It is a complex area but is one that is becoming more prominent given the larger prevalence of HIV. HIV is no longer a death sentence and with current treatments patients can expect to have an almost normal life expectancy. Full knowledge of all the possible interactions is unrealistic but some of the main ones should be kept in mind when prescribing any new medication. There is an excellent resource kept by the University of Liverpool that can be found at <https://www.hiv-druginteractions.org/>

In the case detailed above the patient is likely to have been started on a PPI such as Lansoprazole. Lansoprazole is known to dangerously lower the efficacy of atazanavir and this is exhibited by the dramatic fall in CD4 count. This patient also seems to have developed oesophageal candidiasis and so urgent management to manage his HIV is required to avoid potentially deadly opportunistic infections.

## **HIV: anti-retrovirals**

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- ritonavir: a potent inhibitor of the P450 system

#### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

#### Question 10 of 198

A 45-year-old female presents with a rash. She states that she initially felt feverish and had a runny nose. This progressed to a rash over her arms, trunk and legs. She recently immigrated to the UK from Poland. She lived in a travellers community in Poland and is not aware of any childhood vaccinations. On examination you note a erythematous maculopapular rash over the the upper limbs, thorax and lower limbs.

The following investigations were performed:

Hb	95 g/l	Na <sup>+</sup>	138 mmol/l
Platelets	110 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.8 mmol/l
WBC	3.8 * 10 <sup>9</sup> /l	Urea	6.5 mmol/l
Neuts	1.8 * 10 <sup>9</sup> /l	Creatinine	58 µmol/l
Lymphs	1.6 * 10 <sup>9</sup> /l	CRP	48 mg/l

What is the most likely diagnosis?

[Measles49%](#)[Mumps4%](#)[Rubella13%](#)[Parvovirus B1931%](#)[Scabies3%](#)

Parvovirus B19 can cause fever, rash and pancytopenia (due to an aplastic crisis)

The patient has presented with a febrile rash. The differential is wide. The immunisation history should alert you to possible measles or rubella. However the presence of pancytopenia favours a diagnosis of parvovirus B19 infection which is associated with an aplastic crisis.

#### Parvovirus B19

Parvovirus B19 is a DNA virus which causes a variety of clinical presentations. It was identified in the 1980's as the cause of erythema infectiosum

### **Erythema infectiosum (also known as fifth disease or 'slapped-cheek syndrome')**

The illness may consist of a mild feverish illness which is hardly noticeable. However, in others there is a noticeable rash which appears after a few days. The rose-red rash makes the cheeks appear bright red, hence the name 'slapped cheek syndrome'. The rash may spread to the rest of the body but unlike many other rashes, it only rarely involves the palms and soles.

The child begins to feel better as the rash appears and the rash usually peaks after a week and then fades. The rash is unusual in that for some months afterwards, a warm bath, sunlight, heat or fever will trigger a recurrence of the bright red cheeks and the rash itself. Most children recover and need no specific treatment. In adults, the virus may cause acute arthritis.

Be aware that the virus can affect an unborn baby in the first 20 weeks of pregnancy. If a woman is exposed early in pregnancy (before 20 weeks) she should seek prompt advice from whoever is giving her antenatal care.

It is spread by the respiratory route and a person is infectious 3 to 5 days before the appearance of the rash. Children are no longer infectious once the rash appears and there is no specific treatment.

The child need not be excluded from school as they are no longer infectious by the time the rash occurs.

### **Other presentations**

Other presentations include:

- asymptomatic
- pancytopenia in immunosuppressed patients
- aplastic crises e.g. in sickle-cell disease (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anaemia is rare unless there is a chronic haemolytic anaemia)

Question 1 of 188

A 64-year-old lady with a background of Alzheimer's dementia presents with a 3 day history of increased confusion, lower abdominal pain and foul smelling urine. Blood tests on admission show:

Hb      119 g/l      Na<sup>+</sup>      136 mmol/l

Platelets	425 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.7 mmol/l
WBC	15.9 * 10 <sup>9</sup> /l	Urea	7.2 mmol/l
Neuts	13 * 10 <sup>9</sup> /l	Creatinine	78 µmol/l
Lymphs	2 * 10 <sup>9</sup> /l	CRP	140 mg/l
Eosin	0.02 * 10 <sup>9</sup> /l		

She is started on treatment for a urinary tract infection. 2 days later her blood tests show the following:

Hb	115 g/l	Na <sup>+</sup>	141 mmol/l
Platelets	360 * 10 <sup>9</sup> /l	K <sup>+</sup>	5.2 mmol/l
WBC	10.2 * 10 <sup>9</sup> /l	Urea	8 mmol/l
Neuts	7.5 * 10 <sup>9</sup> /l	Creatinine	105 µmol/l
Lymphs	1.5 * 10 <sup>9</sup> /l	CRP	43 mg/l
Eosin	0.001 * 10 <sup>9</sup> /l		

Which antibiotic was she likely to have been treated with?

[Trimethoprim54%Erythromycin5%Co-amoxiclav6%Nitrofurantoin27%Ciprofloxacin8%](#)

Trimethoprim can lead to an increase in creatinine as they both compete at the same receptor in the tubules for elimination in the urine.

## **Trimethoprim**

Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.

Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase

Adverse effects

- myelosuppression
- transient rise in creatinine: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug



## Question 2 of 188

A 98-year-old lady presents with a fever and confusion and on initial review is started on broad spectrum antibiotics. Despite five days of therapy, her temperature is 38.9°C and her clinical condition seems to have deteriorated. She has no relevant past medical history. The diagnosis of urinary tract infection (UTI) is confirmed when urine cultures confirm an extended spectrum B-lactamase (ESBL) producing *Escherichia coli* (E. coli).

Following the failure to respond to the first-line agent, which antibiotic is most likely to be effective?

[Trimethoprim9%](#) [Tetracycline4%](#) [Amoxicillin5%](#) [Cefalexin11%](#) [Ertapenem72%](#)

Extended spectrum B-lactamase (ESBL) producing organisms are typically resistant to penicillins and cephalosporins and as such the carbapenem class of antibiotics are typically first-line although nitrofurantoin or fosfomycin are also frequently effective. ESBL producers are most commonly *Escherichia coli* (E. coli) and *Klebsiella* species.

### *Escherichia coli*

*Escherichia coli* is a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

*E. coli* infections lead to a variety of diseases in humans including:

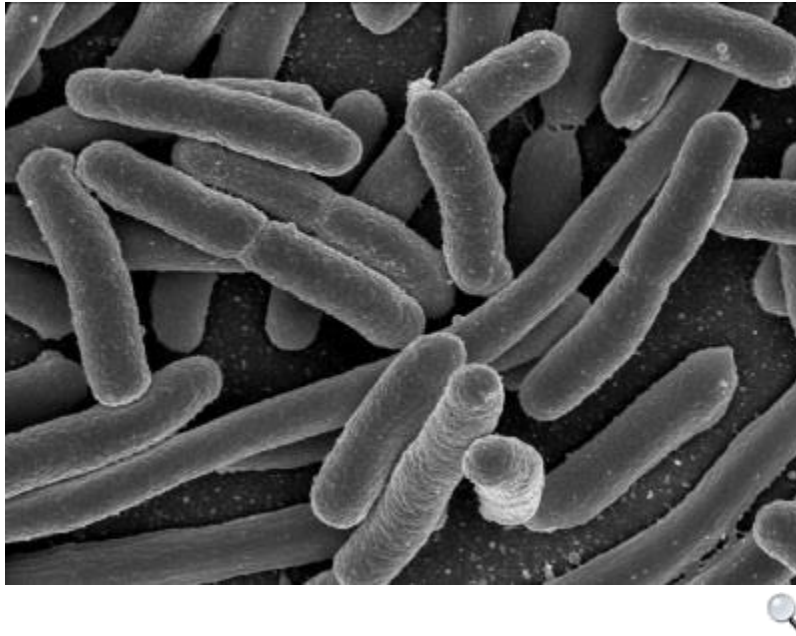
- diarrhoeal illnesses
- UTIs
- neonatal meningitis

### Serotypes

*E. coli* may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to <i>E. coli</i> is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

*E. coli* O157:H7 is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by haemolytic uraemic syndrome. It is often spread by contaminated ground beef.



Scanning electron micrograph of *Escherichia coli*, grown in culture and adhered to a cover slip.  
Credit: NIAID

### Question 3 of 188

A 27-year-old nurse attends the emergency department and reports she has just suffered a significant needle-stick injury while caring for her patient on the intensive care unit. While providing her patient personal care with her colleague, she was injured in the hand by a wide bore stylet needle previously used to introduce an IV cannula to her patient that had not been placed in an appropriate sharps bin. The needle had been visibly blood stained. The nurse had been wearing gloves and had followed correct first aid procedure for needle-stick injuries.

The nurse was very concerned as the patient who had been the needle-stick donor was receiving treatment for the acute neurological phase of rabies. Review of the patients clinical notes (with the consent of the patients next of kin) indicated that he had contracted rabies following a dog bite two months previously in Pakistan. The diagnosis of rabies encephalitis had been made following clinical review by infectious disease experts and the detection of neutralising serum antibodies.

The nurse was previously fit and healthy with no significant past medical history. She did not use any regular medications and had no allergies. She was uncertain if she had had any previous vaccination against rabies, although did recall having a course of injections 10 years previously before she visited family in rural India.

What is the correct management of the needle-stick injury to prevent transmission of rabies?

[Rabies immunoglobulin and full course rabies vaccination](#)57%[Booster course rabies vaccination](#)10%[Rabies immunoglobulin](#)11%[Full course rabies vaccination](#)8%[No action required](#)14%

This situation represents a difficult clinical decision. Humans are considered to be an end-host for the rabies virus as inter-human transmission is not documented outside of transplantation cases. For that reason, only standard infection control precautions are recommended for health-care workers when in contact with individuals with rabies. However, the needle-stick injury described could foreseeably lead to transmission of the virus and given the severe consequences of rabies should be considered as possible rabies exposure.

The patient does not have a clear history of previous immunisation (the history stated could also be consistent with hepatitis B vaccination for example). Rabies immunoglobulin should be given to provide passive antibodies at the site of exposure prior to the development of an immune response. As far as possible, the dose (20 IU / Kg) should be administered locally around the wound. In addition, post-exposure vaccination should be provided, with the WHO currently recommending a four dose schedule (given on days 0, 3, 7 and 14).

If an individual has been previously vaccinated then immunoglobulin is not required and a two dose vaccination schedule (given on days 0 and 3) should be given.

Crowcroft N, Thampi N. The prevention and management of rabies. BMJ 2015;350:g7827.

## **Rabies**

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus (specifically a lyssavirus) and has a bullet-shaped capsid. The vast majority of cases are caused by dog bites but it may also be transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Rabies is estimated to still kill around 25,000-50,000 people across the world each year. The vast majority of the disease burden falls on people in poor rural areas of Africa and Asia. Children are particularly at risk.

## Features

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at-risk countries:

- the wound should be washed
- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination. If possible, the dose should be administered locally around the wound

If untreated the disease is nearly always fatal.

## Question 4 of 188

A 36-year-old Sri-Lankan woman presents to the GP with a malar rash. On examination she has a erythematous rash that is warm to touch with some underlying oedema over both cheeks and the bridge of her nose.

She reports feeling low in energy over several months and describes a feeling of numbness in her feet and hands.

## Investigations:

haemoglobin	125 g/L (115-165)
white cell count	$9.4 \times 10^9/L$ (4.0-11.0)
platelet count	$220 \times 10^9/L$ (150-400)
erythrocyte sedimentation rate	50 mm/1st h (<30)
serum urea	7.0 mmol/L (2.5-7.0)
serum creatinine	105 mol/L (60-110)
serum alanine aminotransferase	17 U/L (5-35)
serum aspartate aminotransferase	26 U/L (1-31)
serum complement C3	80 mg/dL (65-190)

serum complement C4	45 mg/dL (15-50)
serum C-reactive protein	145 mg/L (<10)
anti-double-stranded DNA antibodies	negative
c-ANCA	negative
p-ANCA	negative
antinuclear antibodies	1:20 (negative at 1:20 dilution)

An outpatient rheumatology appointment is arranged and she is started on a course of steroids in the interim. Her symptoms rapidly improve and the rash almost completely resolves however she is left with persistent numbness that appears to be worsening.

What is the most likely underlying diagnosis?

[Granuloma annulare 11%](#)[Annular psoriasis 7%](#)[Systemic lupus erythematosus 15%](#)[Leprosy 48%](#)[Cutaneous leishmaniasis 19%](#)

The diagnosis here is leprosy. Leprosy can present along a spectrum from borderline to leprotamous and can often be mistaken for conditions like psoriasis, SLE and granuloma annulare. The key distinguishing feature is the presence of anaesthetic patches that are present in leprosy but none of the other condition. A full clinical examination is not complete until sensation has been checked over the skin lesions with a microfilament.

The presence of anaesthetic patches should prompt you to look for other hallmarks of disease such as thickened nerves (often easiest to feel are the median nerve in the wrist the common peroneal nerve around the lateral head of the fibula and the ulnar nerve at the elbow.) the loss of hair (in and around lesions and often in the eyebrows) and the presence of neuropathy. Diagnosis is made by demonstrating acid fast bacilli within a cutaneous nerve on microscopy.

The severe skin changes seen with leprosy are not caused by the bacteria themselves but the bodys own immune response towards the bacilli. As a result steroids would improve the physical appearance of skin lesions but at the same time accelerate disease as the bacteria proliferate unhindered. This corresponds to the case outlined above where the patients neurological symptoms worsen yet the skin disease improves on starting steroids.

## Leprosy

Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*.

## Features

- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

The degree of cell mediated immunity determines the type of leprosy a patient will develop.

Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')

- extensive skin involvement
- symmetrical nerve involvement

High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')

- limited skin disease
- asymmetric nerve involvement

## Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine

## Question 5 of 188

A 26-year-old woman presents to the Emergency department some 2 weeks after returning from her honeymoon in the Seychelles. Since returning she has suffered from intermittent abdominal bloating and diarrhoea and feels she has lost a little weight. Physical examination reveals a blood pressure of 118/82 mmHg, and her pulse is 70 and regular. There is mild abdominal distension and her body mass index is 22 kg/m<sup>2</sup>

## Investigations:

Hb	110 g/l	Na <sup>+</sup>	138 mmol/l
Platelets	210 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.0 mmol/l
WBC	11.2 * 10 <sup>9</sup> /l	Urea	6.9 mmol/l
Neuts	8.1 * 10 <sup>9</sup> /l	Creatinine	89 µmol/l
Lymphs	1.5 * 10 <sup>9</sup> /l	CRP	82 mg/l

Albumin 34 g/l

Which of the following is the most appropriate intervention?

[Amoxicillin4%Ciprofloxacin25%Gluten free diet6%Lactose free diet13%Metronidazole51%](#)

The most likely diagnosis, given the trip to a tropical region of Africa, intermittent bloating and diarrhoea, and an elevated CRP, is Giardiasis. Empirical treatment is often given, with either a course of metronidazole or a single dose of 2g tinidazole. Food intolerances may persist, particularly with respect to lactose, for some time after the initial infection.

Amoxicillin and ciprofloxacin would usually be used for listeriosis and campylobacter respectively, and neither infection is likely. Neither a wheat free diet nor a lactose-free diet is indicated given the likelihood of ongoing giardiasis, although many patients may suffer symptoms of lactose intolerance post-giardiasis.

## **Giardiasis**

Giardiasis is caused by the flagellate protozoan *Giardia lamblia*. It is spread by the faeco-oral route

### **Features**

- often asymptomatic
- lethargy, bloating, abdominal pain
- non-bloody diarrhoea
- chronic diarrhoea, malabsorption and lactose intolerance can occur
- stool microscopy for trophozoite and cysts are classically negative, therefore duodenal fluid aspirates or 'string tests' (fluid absorbed onto swallowed string) are sometimes needed

Treatment is with metronidazole

A 32 year old man presents with left lower limb weakness for the past three weeks. Over the past week his condition has got much worse. He has lost his appetite and about six kilograms in the last two months. In the same period he reported recurrent bleeding from the nose.

With the help of three months of nicotine transdermal patches and varenicline he is now no longer actively smoking. He is married and works as a salesman in a pharmaceutical company. For the last year he has been to many destinations around the world as part of his job.

On examination he appeared ill. He was oriented in time, place, and person, but was mentally slow in understanding commands during examination. The power in the left leg was grade 2 for all muscle groups. Tone, sensation, coordination and reflexes were all normal. The right leg was normal. No abnormality detected in other systems. The following investigation were ordered:

Hb	10g/dl
Platelets	$10 \times 10^9/l$
WBC	$4 \times 10^9/l$
Neutrophils	60%
Lymphocytes	34%
Na+	135 mmol/l
K+	4 mmol/l
Creatinine	95 $\mu$ mol/l
Urea	4 mmol/l

Urine analysis: Clear

MRI brain showed bilateral multiple hyperintense demyelinating lesions involving sub cortical areas without any mass effect.

What is the most appropriate thing to do?

[CSF analysis for oligoclonal bands13% Brain biopsy7% CSF analysis for herpes simplex virus \(HSV\)14% HIV test50% Stop varenicline16%](#)

The progressive neurological symptoms with demyelination on MRI points to progressive multifocal leukoencephalopathy (PML).

PML is a demyelinating disease of the CNS due to the JC virus. It occurs almost exclusively in immunosuppressed individuals with the majority of cases being secondary to HIV infection. Patients typically experience insidious onset of focal symptoms that include mainly behavior, cognitive, speech, and motor functions. Polymerase chain reaction (PCR) of the CSF has a high sensitivity and specificity for the detection of JC virus in patients with PML.

Neither the symptoms nor the signs are compatible with either multiple sclerosis or HSV.



Varenicline could cause low platelets and appetite changes with psychiatric manifestation. But it would not explain the motor deterioration nor the cognitive decline for this patient.

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



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Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



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Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



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Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
Thallium SPECT negative	Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 2 of 183

A 23-year-old man presents to the emergency department with a fever and a rash having recently returned back from a back-packing trip in rural Thailand where he had been trekking. He complains of general malaise for the last few days, a frontal headache and a rash he has noticed from last night. On examination he had tender cervical lymphadenopathy and a maculopapular rash over his trunk. There was also a small painless erythematous lesion on his lower calf with a necrotic centre.

Hb        95 g/l

Platelets  $60 \times 10^9/l$   
WBC  $2.5 \times 10^9/l$

What is the most likely diagnosis?

[Malaria4%Dengue fever23%Scrub typhus57%Leptospirosis9%HIV conversion illness7%](#)

The eschar makes scrub typhus the most likely diagnosis. Malaria is of course common in this region and one would expect similar laboratory results, however the rash makes this diagnosis very unlikely. Dengue fever presents with a rash and fever, but also with associated arthropathy, classically lower back pain.

## **Typhus**

### Overview

- rickettsial diseases
- transmitted between hosts by arthropods
- cause widespread vasculitis

### Features

- fever, headache
- black eschar at site of original inoculation
- rash e.g. maculopapular or vasculitis
- complications: deranged clotting, renal failure, DIC

### Rocky Mountain spotted fever

- caused by *R. rickettsii*
- initially macular rash on hands and feet then spreads

### Tick typhus

- caused by *R. conorii*
- rash initially in axilla then spreads

### Question 3 of 183

A 23-year-old man presents to the emergency department with shortness of breath, fever and a cough. He has been having a non-productive cough for two weeks. Prior to this, he felt had felt unwell with muscle aches and malaise. He went to his GP and was given amoxicillin but this has made no difference and now he is feeling more breathless and unwell. He has not been outside of the UK in the last year. He has no other medical problems and takes no regular medications. His cough is non-productive and comes in paroxysms which make him concerned.

On examination, there are a few bilateral crepitations but the examination is otherwise normal. His observations show fever and mild hypoxia. Blood tests show mild anaemia and raised inflammatory markers. A chest X-ray shows bilateral consolidation, but he improves with IV co-amoxiclav and clarithromycin over a few days. What is the most likely causative organism?

[Klebsiella pneumoniae8% Legionella pneumophila10% Mycoplasma pneumoniae70% Chlamydia psittaci6% Coxiella burnetii6%](#)

The correct answer is *Mycoplasma pneumoniae*. There are several hints in this history and investigations to suggest *Mycoplasma pneumoniae* as the likely cause. First of all, he is a young and fit patient who describes a non-productive cough preceded by flu-like symptoms and not responding to penicillins. Secondly, he has anaemia which may be due to haemolysis, and finally there is bilateral consolidation on the chest X-ray. *Klebsiella pneumoniae* is more typical in alcoholics, *Legionella pneumophila* is associated with a history of foreign travel, *Chlamydia psittaci* is associated with contact and exposure to birds and finally *Coxiella burnetii* is rare and associated with farm animal exposure.

### ***Mycoplasma pneumoniae***

*Mycoplasma pneumoniae* is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

### Features

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray

- complications may occur as below

## Complications

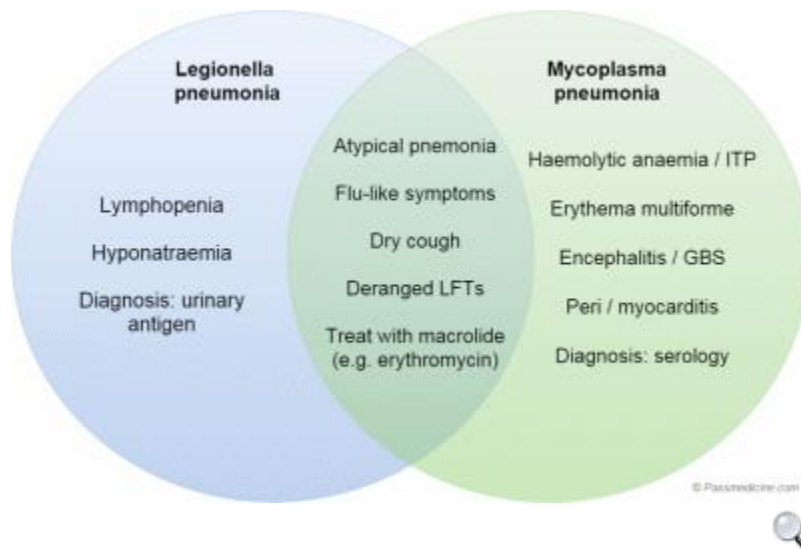
- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

## Investigations

- diagnosis is generally by Mycoplasma serology
- positive cold agglutination test

## Management

- erythromycin/clarithromycin
- tetracyclines such as doxycycline are an alternative



## Comparison of Legionella and Mycoplasma pneumonia



Question 4 of 183

A 31-year-old gentleman presents with fever, headache, abdominal pain and a rash on the chest 3 weeks after visiting South America.

On examination the temperature is 38.2°C. There is a rash on the chest consisting of rose-coloured blanching papules. The respiratory rate is 20 breaths/min and the heart rate is 58 beats per minute. The chest is clear to auscultation. The abdomen is diffusely tender and there is mild splenomegaly.

Initial blood results are as follows:

Hb	128 g/l
Platelets	184 * 10 <sup>9</sup> /l
WBC	3.9 * 10 <sup>9</sup> /l
Na <sup>+</sup>	131 mmol/l
K <sup>+</sup>	3.3 mmol/l
Urea	7.2 mmol/l
Creatinine	141 µmol/l
Bilirubin	46 µmol/l
ALP	147 u/l
ALT	96 u/l
Albumin	38 g/l
CRP	52 mg/l

What is the most appropriate initial antimicrobial therapy?

[Ampicillin14%Chloramphenicol16%Trimethoprim-sulfamethoxazole23%Cefotaxime36%Streptomycin11%](#)

This is a fairly classical presentation of typhoid fever, also known as enteric fever. This is a potentially fatal multisystemic illness caused primarily by *Salmonella enterica*.

The rash here refers to rose spots which occur in up to 30% of people infected with this organism. Characteristically, rose spots are seen in untreated typhoid fever. They usually occur between the second and fourth week of the illness. They characteristically present as groups of 5-15 pink blanching papules distributed between the level of the nipples and umbilicus.

The treatment of choice is cefotaxime or ceftriaxone.

Ciprofloxacin may be used as an alternative in sensitive organisms.

## *Salmonella*

The *Salmonella* group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi* (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, arthralgia

### Features

- initially systemic upset as above
- relative bradycardia
- abdominal pain, distension
- constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid
- rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

### Possible complications include

- osteomyelitis (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%, more likely if adult females)

### Question 5 of 183

A 27-year-old male presents with high-grade fever and vomiting for 8 days. He recently went to Africa for a jungle safari with a group of friends and began feeling unwell whilst he was there. During the trip, he spent most of the time camping outdoors. He does not have any history of fits or loss of consciousness, although he has been feeling drowsy and complains of generalised malaise. He also has pain in his wrist and shoulder joints but they are not swollen. He takes alcohol regularly and smokes cannabis socially.

On examination, he has a fever of 39°C and a pulse of 135bpm. His blood pressure is 100/70mmHg. He is icteric but does not have any flapping tremors. There is evidence of an

enlarged spleen which is palpable 3 finger breadths below the left costal margin. The liver span is normal.

Lab reports reveal:

Hb 115 g/l  
Platelets  $100 \times 10^9/l$   
WBC  $9.5 \times 10^9/l$   
Reticulocytes 5% (0.2 - 2%)

Na<sup>+</sup> 140 mmol/l  
K<sup>+</sup> 4.6 mmol/l  
Urea 5.1 mmol/l  
Creatinine 83  $\mu$ mol/l

Bilirubin 49  $\mu$ mol/l  
AST 50 u/l  
ALT 25 u/l  
Glucose 6.0 mmol/l

CT scan brain: Normal

CSF examination reveals:

Appearance Clear  
Protein 0.3 g/L (0.2-0.4 g/L)  
Glucose 5.3 mmol/l  
Lymphocytes 15/mm<sup>3</sup>  
Neutrophils 10

Which of the following is the most appropriate treatment option?

[Chloroquine 14% Artemether/lumefantrine 56% Primaquine 14% IV acyclovir 9% Co-trimoxazole 7%](#)

The high-grade fever, history of travel to an endemic area, splenomegaly, thrombocytopaenia, evidence of haemolysis (raised bilirubin and reticulocytosis) and normal blood leucocyte count all favour a diagnosis of cerebral malaria

The treatment modality most suited would be a combination of artemether and lumefantrine which would provide adequate coverage from plasmodium falciparum.

Diagnosis is through examination of blood films (thick and thin films) for evidence of

parasitaemia and the ICT-MP.

The CSF findings are non-specific with the only abnormality being a mild lymphocytosis which is of no bearing on the scenario. It, however, rules out bacterial or tuberculous meningitis.

The mildly raised AST is in keeping with his history of alcohol intake.

## **Malaria: Falciparum**

Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 °C
- severe anaemia
- complications as below

Complications

- cerebral malaria: seizures, coma
- acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
- acute respiratory distress syndrome (ARDS)
- hypoglycaemia
- disseminated intravascular coagulation (DIC)

Uncomplicated falciparum malaria

- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

Severe falciparum malaria

- a parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

#### Question 6 of 183

A 25-year-old HIV-positive male goes to his GP with complaints of headache and left-sided weakness of recent onset. His temperature is 38°C, blood pressure is 115/70 mmHg, respirations are 14/min and pulse is 73/min.

Neurological examination reveals decreased power, hyperreflexia in the left upper and lower limb with associated upgoing plantars. CT head shows multiple ring-enhancing lesions.

What is the most appropriate next step in management?

[Trimethoprim-sulfamethoxazole 10% Sulfadiazine and pyrimethamine 79% Brain irradiation 3% Brain biopsy 3% Start albendazole 5%](#)

The most common cause of central nervous system mass lesion in AIDS patients is toxoplasmosis. This patient's findings are consistent with cerebral toxoplasmosis. Trimethoprim-sulfamethoxazole is used for prophylaxis of toxoplasmosis, while sulfadiazine and pyrimethamine are used for treatment purposes.

Choice 3: Brain irradiation is used in the management of primary CNS lymphoma. Patients with primary CNS lymphoma are usually afebrile; lesions are weakly enhancing and are single (can be multiple). This is suspected if the patient does not respond to antibiotic therapy.

Choice 4: Brain biopsy is reserved for patient's whose lesions do not respond to treatment with sulfadiazine and pyrimethamine.

Choice 5: Albendazole is used for neurocysticercosis. This condition is not usually seen in AIDS patients.

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



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Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



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Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



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Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.





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Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
Thallium SPECT negative	Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 7 of 183

A 24-year-old lady presents 16 weeks pregnant. She complains of myalgia, sore throat and coryza and is noted to have a pyrexia of 38.1. She works in a nursing home which is currently closed due to an influenza A outbreak. On further questioning, you note that she has been vomiting every morning for the past 8 weeks and is no longer able to take oral medication. On examination her chest is clear but she is obviously coryzal with an erythematous oropharynx (no exudate). Chest X-ray is clear. Apart from informing the obstetrics team, how would you manage this patient?

[Admit, isolate and commence oseltamivir 27%](#) [Admit and observe 9%](#) [Oral antibiotics 5%](#) [Admit, isolate and commence zanamivir 39%](#) [Admit, isolate and await nose and throat swabs before commencing antiviral therapy 20%](#)

This patient has had known exposure to influenza A. She should be admitted for observation and immediately commenced on empirical treatment. NICE recommends oseltamivir treatment as first line for suspected or confirmed influenza A in pregnancy. However, given that this patient has been vomiting, zanamivir (intranasal/intravenous) should be used in preference to oral Tamiflu (oseltamivir). Empirical treatment should be commenced immediately and not withheld until the results of swabs are available.

There may be a role for antibiotics if there is a co-existing infection or evidence of pneumonia on chest X-ray.

## Antiviral agents

Drug	Mechanism of action	Indications	Adverse effects/toxicity
<b>Aciclovir</b>	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	HSV, VZV	Crystalline nephropathy
<b>Ganciclovir</b>	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	CMV	Myelosuppression/agranulocytosis
<b>Ribavirin</b>	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA	Chronic hepatitis C, RSV	Haemolytic anaemia
<b>Amantadine</b>	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech
<b>Oseltamivir</b>	Inhibits neuraminidase	Influenza	
<b>Foscarnet</b>	Pyrophosphate analog which inhibits viral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnasaemia, seizures
<b>Interferon-</b>	Human glycoproteins which	Chronic	Flu-like symptoms, anorexia,

<b>Drug</b>	<b>Mechanism of action</b>	<b>Indications</b>	<b>Adverse effects/toxicity</b>
<b><math>\alpha</math></b>	inhibit synthesis of mRNA	hepatitis B & C, hairy cell leukaemia	myelosuppression
<b>Cidofovir</b>	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir)	CMV retinitis in HIV	Nephrotoxicity

### **Anti-retroviral agent used in HIV**

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine

Protease inhibitors (PI)

- inhibits a protease needed to make the virus able to survive outside the cell
- examples: indinavir, nelfinavir, ritonavir, saquinavir

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz

Question 3 of 176

A 28-year-old man who has recently immigrated from Nigeria presents with a penile ulcer. He reports that it initially started as a small lump but then later progressed to a painful ulcer.

On examination, there is a 7mm diameter tender single ulcer with an undermined ragged edge just proximal to the glans of the penis. Examination of the testes and anal region is unremarkable. There is tender inguinal lymphadenopathy.

What is the most likely diagnosis?

[Syphilis7%Herpes simplex virus10%Granuloma inguinale13%Lymphogranuloma venereum32%Chancroid38%](#)

Chancroid is a bacterial sexually transmitted infection characterised by painful sores on the genitalia. It is caused by the gram-negative coccobacillus *Haemophilus ducreyi*. It is a disease found primarily in developing countries.

*H. ducreyi* enters the skin through microabrasions incurred during sexual intercourse. A local tissue reaction leads to the development of an erythematous papule, which progresses to a pustule in 4-7 days. It then undergoes central necrosis to ulcerate.

The ulcer can range in size from 3 to 50 mm across. It is painful and has sharply defined undermined borders

Other features include:

- Irregular or ragged borders
- A base that is covered with a grey or yellowish-gray material
- A base that bleeds easily if traumatised or scraped
- Painful lymphadenopathy in 30 to 60% of patients.
- Dysuria and dyspareunia in females

About half of infected men have only a single ulcer. Women frequently have four or more ulcers, with fewer symptoms.

## **STI: ulcers**

Genital herpes is most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1). Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site

Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. Infection is characterised by primary, secondary and tertiary stages. A painless ulcer (chancre) is seen in the primary stage. The incubation period= 9-90 days

Chancroid is a tropical disease caused by *Haemophilus ducreyi*. It causes painful genital ulcers associated with unilateral, painful inguinal lymph node enlargement. The ulcers typically have a sharply defined, ragged, undermined border.

Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis*. Typically infection comprises of three stages

- stage 1: small painless pustule which later forms an ulcer
- stage 2: painful inguinal lymphadenopathy
- stage 3: proctocolitis

LGV is treated using doxycycline.

Other causes of genital ulcers

- Behcet's disease
- carcinoma
- granuloma inguinale: *Klebsiella granulomatis*\*

\*previously called *Calymmatobacterium granulomatis*

#### Question 1 of 173

A 68-year-old man presents to hospital with progressive shortness of breath over the last four days and a low-grade fever. He has a past medical history of mild asthma for which he occasionally needs to use his salbutamol inhaler and has previously had bilateral knee replacements for osteoarthritis. He has smoked on average 5 cigarettes per day for the past 40 years and drinks a couple of glasses of wine per week. His travel history includes a holiday to Cyprus, from which he arrived back in the UK 5 days ago.

Examination revealed some right mid zone crackles and reduced breath sounds over this area. Observations revealed a temperature of 38.8°C, heart rate of 110 bpm, blood pressure of 105/66 mmHg, respiratory rate of 22 breaths per minute and oxygen saturations of 91% on room air.

Blood tests revealed:

Hb	145 g/l
Platelets	290 * 10 <sup>9</sup> /l
WBC	9.4 * 10 <sup>9</sup> /l
Na <sup>+</sup>	132 mmol/l
K <sup>+</sup>	3.7 mmol/l
Urea	4.1 mmol/l
Creatinine	67 µmol/l

Urinary sodium concentration was measured and found to be 36mmol/L (normal range 40-220 mmol/d). Which of the following investigations is most useful in the diagnosis of this condition?

Urine antigen test 77% Serum antibody test 8% Sputum PCR 6% CT pulmonary angiography 5% D-dimer 5%

This scenario is most likely due to the organism *Legionella pneumophila* (causing Legionnaire's disease) - an infection which is often due to air conditioning units and heating units. This patient may have got the infection when on holiday and his sodium is low, often a result of syndrome of inappropriate ADH secretion. The most accurate investigation for Legionella infection is via the urine antigen test, which is quick and specific.

### ***Legionella***

Legionnaire's disease is caused by the intracellular bacterium *Legionella pneumophila*. It is typically colonizes water tanks and hence questions may hint at air-conditioning systems or foreign holidays. Person-to-person transmission is not seen

#### Features

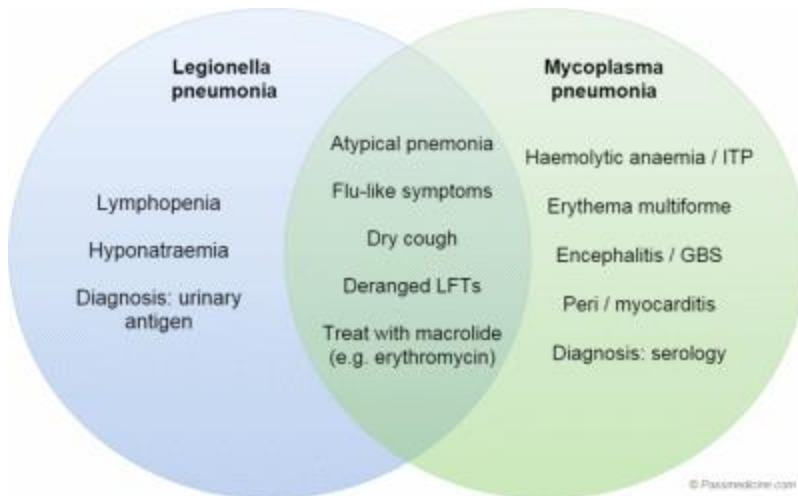
- flu-like symptoms including fever (present in > 95% of patients)
- dry cough
- relative bradycardia
- confusion
- lymphopaenia
- hyponatraemia
- deranged liver function tests
- pleural effusion: seen in around 30% of patients

#### Diagnosis

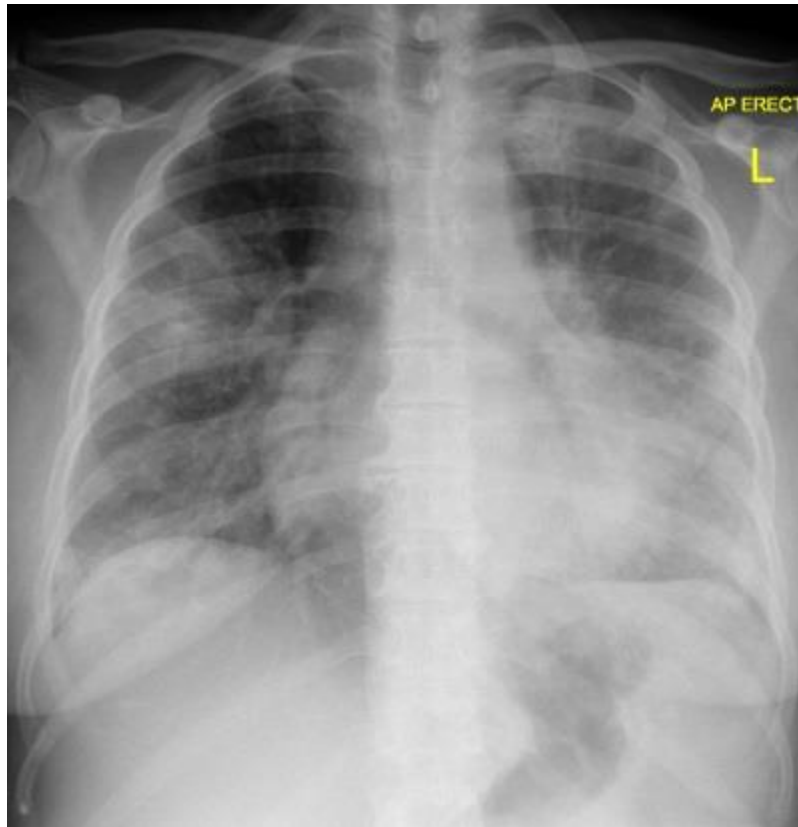
- urinary antigen

#### Management

- treat with erythromycin



### Comparison of Legionella and Mycoplasma pneumonia



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Chest x-ray features of legionella pneumonia are non-specific but includes a mid-to-lower zone predominance of patchy consolidation. Pleural effusions are seen in around 30%.



### Question 2 of 173

An 18-year-old man from Bangladesh presents to the emergency department with shortness of breath that has been worsening over the last couple of hours. A friend reports that he has had a sore throat over the last couple of days and that he was found in his room having shortness of breath and a fever, which is why she brought him into the emergency department. He does not have any relevant past medical history and family history is unknown.

His observations revealed a temperature of 39.2°C, a respiratory rate of 28 breaths per minute, an oxygen saturations of 92% on 15L of oxygen, a heart rate of 118 beats per minute and a blood pressure of 95/40 mmHg. Examination revealed stridor throughout the chest and the man was sweaty and had signs of peripheral cyanosis.

What is the most appropriate next step in this patient's treatment?

[Intravenous corticosteroids15%](#) [Intravenous adrenaline7%](#) [Endotracheal intubation51%](#) [Intramuscular adrenaline19%](#) [Intravenous antibiotics8%](#)

The most likely diagnosis in this scenario is acute epiglottitis and early endotracheal intubation is vital before the air becomes more obstructed.

### Acute epiglottitis

Acute epiglottitis is rare but serious infection caused by *Haemophilus influenzae* type B. Prompt recognition and treatment is essential as airway obstruction may develop. Epiglottitis was generally considered a disease of childhood but in the UK it is now more common in adults due to the immunisation programme. The incidence of epiglottitis has decreased since the introduction of the Hib vaccine

#### Features

- rapid onset
- high temperature, generally unwell
- stridor
- drooling of saliva

### Question 3 of 173

A 55-year-old woman is referred for an urgent assessment by the infectious diseases team after presenting to her local out of hours GP. The patient stated that she was concerned about having caught Lyme disease during a recent day out in the New Forest in Hampshire, UK. The patient was particularly concerned about this diagnosis as she had a close friend who had been forced to give up work after suffering from neuroborreliosis.

On closer questioning, the patient reported that 2 days previously she had gone on a walk in the New Forest. When she had arrived home that evening she had found two engorged ticks attached to her right lower leg. Her husband had removed the ticks by applying nail polish to them and then pulling them off with tweezers.

The patient denied suffering from any symptoms at the time of presentation though admitted she was very anxious. In particular, the patient had not experienced any neurological or cardiovascular symptoms and had not observed any skin rashes.

The patient was receiving treatment from her GP for hypercholesterolaemia and mild asthma. The patient had no known drug allergies and was employed as a legal secretary at a local firm.

A full examination of the patient's skin was performed and no abnormal rashes or other skin changes were identified. No focal neurology was identified on examination of the peripheral and central nervous systems. The assessment did not identify any signs of meningism. The patient was afebrile.

What is the appropriate management of this patient's tick bites?

[Treat with amoxicillin for 14 days5%Immediate serological testing for pathogenic \*Borrelia\* species10%Serological testing for pathogenic \*Borrelia\* species in 4 weeks \(to allow for seroconversion\)14%No investigation or treatment indicated at present time, carefully observe for onset of symptoms48%Treat with doxycycline for 14 days22%](#)

This patient has a convincing history for the attachment of ticks from a region of the UK at high risk of Lyme borreliosis. When assessing the risk of tick bites it is important to clarify for how long the tick was attached and if it became engorged. Transmission of pathogenic *Borrelia* species is unlikely if ticks are attached for less than 24 hours or do not become engorged. Ticks should be removed gently using tweezers to minimise irritation to the skin and the risk of rupturing the tick which can increase the risk of infection.

Asymptomatic patients who report a tick bite should not undergo serological testing or receive treatment. Testing can lead to false positives secondary to previous infection or cross-reactive antibodies. Prophylactic treatment of tick bites may be required if the patient is immunosuppressed or in certain regions of the USA where the prevalence of infected ticks is particularly high.

When serological testing is indicated paired blood samples should be taken at four week intervals

to allow seroconversion to take place. Treatment with doxycycline or amoxicillin for 14 days is the appropriate treatment for a patient presenting with erythema migrans after a tick bite.

Duncan C, Carle G, Seaton R. Tick bite and early Lyme borreliosis. *BMJ* 2012;344:e3124.

## **Lyme disease**

Lyme disease is caused by the spirochaete *Borrelia burgdorferi* and is spread by ticks

### Features

- early: erythema chronicum migrans + systemic features (fever, arthralgia)
- CVS: heart block, myocarditis
- neuro: cranial nerve palsies, meningitis

### Investigation

- serology: antibodies to *Borrelia burgdorferi*. These can take 3-8 weeks before they are detectable

### Management

- doxycycline if early disease. Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
- ceftriaxone if disseminated disease
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

### Question 5 of 173

A 43-year-old man with advanced HIV is admitted to the Emergency Department with dyspnoea. For the past two weeks he has been getting increasingly short-of-breath on even minimal exertion.

On admission his temperature was 37.7°C, pulse 96/min, oxygen saturations 92% on room air and blood pressure 110/68 mmHg. Auscultation of the chest revealed scattered crackles bilaterally.

An chest x-ray down on admission showed minimal bilateral pulmonary infiltrates. A few hours after admission his dyspnoea worsens. At CT chest is shown below:



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What is the cause his worsening symptoms?

[Pneumothorax57%](#)[Pneumocystis jiroveci-related empyema18%](#)[Collapse of right middle lobe secondary to mucous plugging9%](#)[Miliary tuberculosis4%](#)[Pulmonary cryptococcosis with bullae formation11%](#)

The underlying diagnosis here is *Pneumocystis jiroveci* pneumonia. A history of advanced HIV, exertional dyspnoea combined with non-specific examination and chest x-ray findings is in keeping with the diagnosis. Pneumothorax is a common complication of *Pneumocystis jiroveci* pneumonia and explains the patients deterioration.

## **HIV: *Pneumocystis jiroveci* pneumonia**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count  $< 200/\text{mm}^3$  should receive PCP prophylaxis

### Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

### Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

### Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if  $\text{pO}_2 < 9.3\text{kPa}$  then steroids reduce risk of respiratory failure by 50% and death by a third)



© Image used on license from [Radiopaedia](http://radiopaedia.org)

CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

Question 6 of 173

A 33-year-old gentleman attends a routine sexual health clinic screen and is found to be HIV positive, with a CD4 count of 900 cells/mm<sup>3</sup>. He remains asymptomatic. What is the recommended next best step in terms of treatment?

[Start antiretrovirals when CD4 count reaches 350 cells/mm<sup>3</sup> or less](#)5% [Start antiretrovirals when CD4 count reaches 500 cells/mm<sup>3</sup> or less](#)4% [Start antiretrovirals when becomes symptomatic](#)4% [Start antiretrovirals immediately](#)83% [Start antiretrovirals when CD4 count reaches 250 cells/mm<sup>3</sup> or less](#)4%

Viral load is the single greatest determinant of the risk of HIV transmission. When someone is virally suppressed (viral load is undetectable), the risk of HIV transmission is significantly reduced. Antiretrovirals (ART) reduce HIV transmission by lowering viral load and the evidence now supports early initiation of ART irrespective of CD4 count (WHO 2015 guidelines).

<http://apps.who.int/iris/bitstream/10665/246200/1/9789241511124-eng.pdf?ua=1>

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

### Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

### Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

## Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

### Question 9 of 173

A 38 year-old intravenous drug user presented to accident and emergency with a 10-day history of severe watery diarrhoea and abdominal cramps. Her past medical history included treatment for a groin abscess 3 years previously. She could not remember ingesting any possible causative food and had not travelled abroad. She smoked 15 cigarettes per day and drank 30-40 units of alcohol per week.

On examination, her temperature was 36.8°C, heart rate 100 beats per minute, blood pressure 92/58 mmHg, respiratory rate 18 breaths per minute and oxygen saturations 100% on room air. Her tongue appeared dry with white patches evident on the hard palate and throat. The JVP was not visible. Her chest was clear on auscultation and heart sounds were normal. The abdomen was soft on palpation with some mild central abdominal tenderness.

### Investigations:

Haemoglobin	170 g/L
White cell count	$4.5 \times 10^9/l$
Neutrophil count	$3.0 \times 10^9/l$
Lymphocyte count	$0.1 \times 10^9/l$
Eosinophil count	$0.4 \times 10^9/l$
Platelets	$423 \times 10^9/l$

Sodium	132 mmol/l
Potassium	3.0 mmol/L
Urea	13.0 mmol/L
Creatinine	110 mol/L
Alkaline phosphatase	57 IU/L
Alanine aminotransferase	60 IU/L
Gamma-glutyl transferase	67 IU/L
Bilirubin	19 mol/L
Albumin	29 g/L

Abdominal x-ray: No abnormality detected



Stool culture: No growth at 48 hours

What additional staining technique should be used for analysing the stool sample?

[Ziehl-Neelson36%Romanowsky8%Periodic acid-Schiff23%Sudan12%Silver21%](#)

This patient is likely to have *Cryptosporidium parvum* infection. In the immunocompetent, the protozoan causes a self-limiting diarrhoeal illness lasting 7-10 days or may even be asymptomatic. However, in this case there is likely to be co-existing immunosuppression from human immunodeficiency virus infection, which can result in a severe cholera-like diarrhoea syndrome. The most appropriate staining technique in this case is a modified acid-fast stain such as Ziehl-Neelson, which will stain *C. parvum* oocysts red. Periodic acid-schiff is used on jejunal biopsy specimens to diagnose Whipples disease. Silver staining can pick up *Pneumocystis jiroveci* on sputum samples. Sudan stain is used to diagnose steatorrhoea, and Romanowsky is a blood staining method which preceded Giemsa staining.

## **HIV: diarrhoea**

Diarrhoea is common in patients with HIV. This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections

Possible causes

- *Cryptosporidium* + other protozoa (most common)
- Cytomegalovirus
- *Mycobacterium avium intracellulare*
- *Giardia*

*Cryptosporidium* is the most common infective cause of diarrhoea in HIV patients. It is an intracellular protozoa and has an incubation period of 7 days. Presentation is very variable, ranging from mild to severe diarrhoea. A modified Ziehl-Neelsen stain (acid-fast stain) of the stool may reveal the characteristic red cysts of *Cryptosporidium*. Treatment is difficult, with the mainstay of management being supportive therapy\*

*Mycobacterium avium intracellulare* is an atypical mycobacteria seen with the CD4 count is below 50. Typical features include fever, sweats, abdominal pain and diarrhoea. There may be hepatomegaly and deranged LFTs. Diagnosis is made by blood cultures and bone marrow examination. Management is with rifabutin, ethambutol and clarithromycin

\*nitazoxanide is licensed in the US for immunocompetent patients

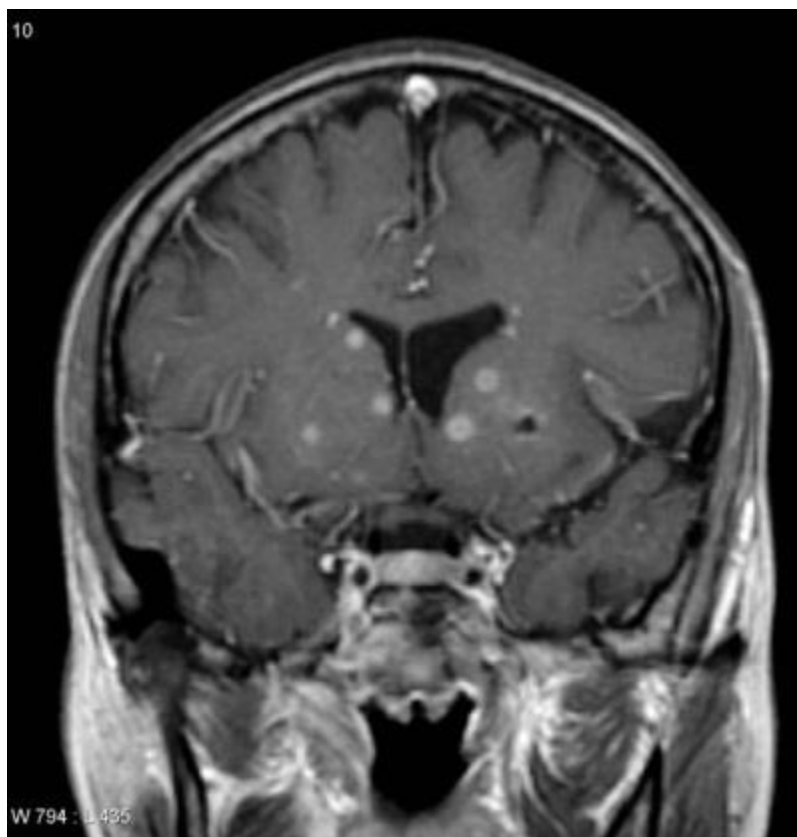
Question 7 of 173

A 33-year-old man who has recently emigrated from Zimbabwe is admitted after being found confused at home. His partner reports that he has been acting strangely for a number of weeks and complaining of altered taste and dizziness. She reports that she is HIV positive but her partner refuses to be tested as he does not believe in 'medical lies'.

On admission he is afebrile with a blood pressure of 114/82mmHg and pulse 78/min.

Rapid HIV testing confirms that he has the infection. His CD4 count is 11 cells/ $\mu$ l.

An MRI (T1 C+) shows the following:



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Other than starting highly active antiretroviral treatment, what is the most appropriate treatment?

[Amphotericin B 16%](#)[Surgical resection 5%](#)[Steroids + methotrexate + whole brain irradiation 8%](#)[Rifampicin + isoniazid + pyrazinamide + ethambutol + steroids 11%](#)[Sulfadiazine + pyrimethamine 61%](#)

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



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Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



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Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
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Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 8 of 173

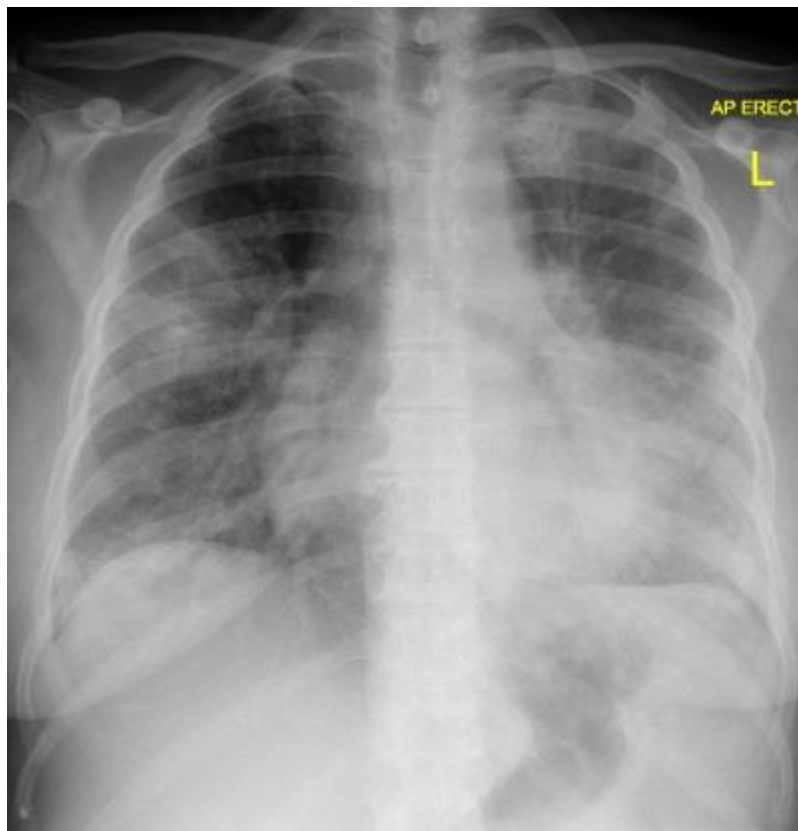
A 54-year-old woman presents to the Acute Medical Unit with a three day history of fever, myalgia and a non-productive cough. She initially thought her symptoms were due to the 'flu but over the past 24 hours has been feeling progressively more poorly. She now also has nausea, abdominal pain, headaches and diarrhoea.

On examination her pulse is 84/min, temperature 39.4°C and blood pressure 106/76 mmHg. Bilateral scattered crackles are noted on auscultation.

Bloods show the following:

Hb	12.4 g/l	Na <sup>+</sup>	133 mmol/l
Platelets	363 * 10 <sup>9</sup> /l	K <sup>+</sup>	5.0 mmol/l
WBC	12.1 * 10 <sup>9</sup> /l	Urea	7.8 mmol/l
Neuts	10.8 * 10 <sup>9</sup> /l	Creatinine	88 µmol/l
Lymphs	1.1 * 10 <sup>9</sup> /l	CRP	145 mg/l
Eosin	0.2 * 10 <sup>9</sup> /l		

The chest x-ray is shown below:



© Image used on license from [Radiopaedia](#)



Which investigation is most likely to be diagnostic?

[Sputum culture](#)7%[Cold agglutinins](#)14%[Bronchoalveolar lavage](#)9%[Blood serology](#)18%[Urinary antigen](#)52%

The chest x-ray shows the asymmetrical, patchy bilateral consolidation typical of *Legionella*.



This combined with high fever, hyponatraemia, abdominal pain and lymphopaenia make the diagnosis the most likely.

### ***Legionella***

Legionnaire's disease is caused by the intracellular bacterium *Legionella pneumophila*. It is typically colonizes water tanks and hence questions may hint at air-conditioning systems or foreign holidays. Person-to-person transmission is not seen

#### Features

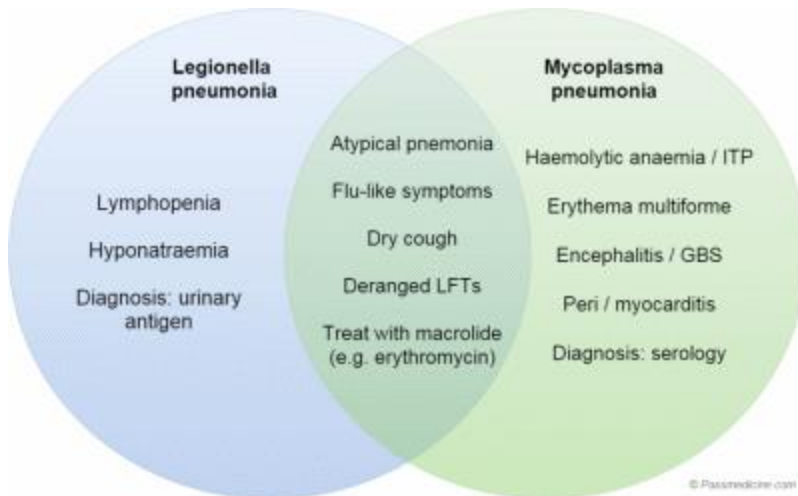
- flu-like symptoms including fever (present in > 95% of patients)
- dry cough
- relative bradycardia
- confusion
- lymphopaenia
- hyponatraemia
- deranged liver function tests
- pleural effusion: seen in around 30% of patients

#### Diagnosis

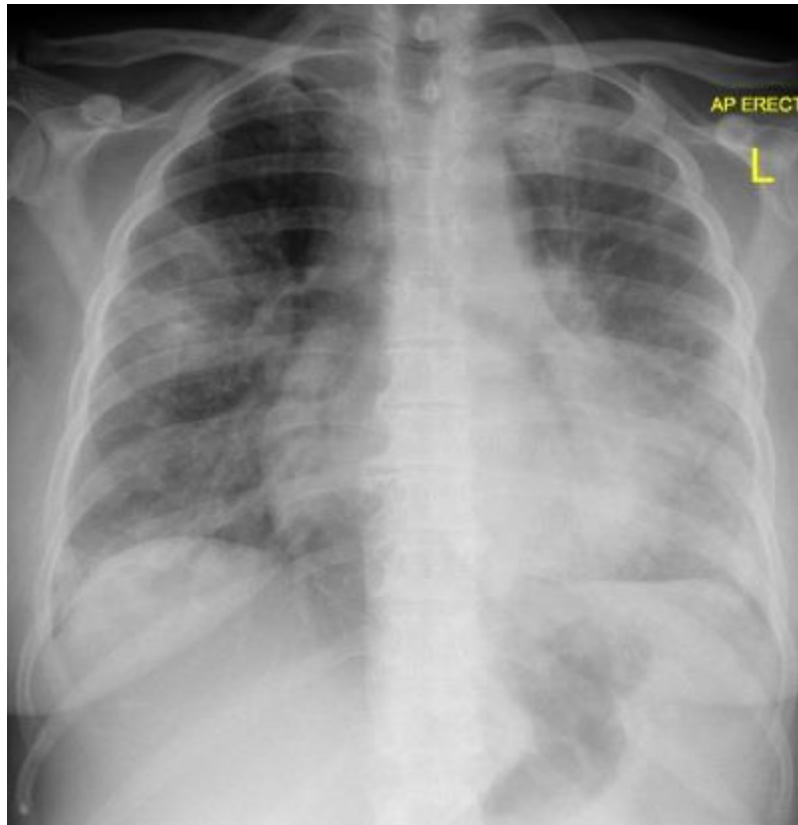
- urinary antigen

#### Management

- treat with erythromycin



### Comparison of Legionella and Mycoplasma pneumonia



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Chest x-ray features of legionella pneumonia are non-specific but includes a mid-to-lower zone predominance of patchy consolidation. Pleural effusions are seen in around 30%.

Question 9 of 173

A 38 year-old intravenous drug user presented to accident and emergency with a 10-day history of severe watery diarrhoea and abdominal cramps. Her past medical history included treatment for a groin abscess 3 years previously. She could not remember ingesting any possible causative food and had not travelled abroad. She smoked 15 cigarettes per day and drank 30-40 units of alcohol per week.

On examination, her temperature was 36.8°C, heart rate 100 beats per minute, blood pressure 92/58 mmHg, respiratory rate 18 breaths per minute and oxygen saturations 100% on room air. Her tongue appeared dry with white patches evident on the hard palate and throat. The JVP was not visible. Her chest was clear on auscultation and heart sounds were normal. The abdomen was soft on palpation with some mild central abdominal tenderness.

Investigations:

Haemoglobin	170 g/L
White cell count	$4.5 \times 10^9/l$
Neutrophil count	$3.0 \times 10^9/l$
Lymphocyte count	$0.1 \times 10^9/l$
Eosinophil count	$0.4 \times 10^9/l$
Platelets	$423 \times 10^9/l$

Sodium	132 mmol/l
Potassium	3.0 mmol/L
Urea	13.0 mmol/L
Creatinine	110 mol/L
Alkaline phosphatase	57 IU/L
Alanine aminotransferase	60 IU/L
Gamma-glutyl transferase	67 IU/L
Bilirubin	19 mol/L
Albumin	29 g/L

Abdominal x-ray: No abnormality detected

Stool culture: No growth at 48 hours

What additional staining technique should be used for analysing the stool sample?

[Ziehl-Neelson36%](#)[Romanowsky8%](#)[Periodic acid-Schiff23%](#)[Sudan12%](#)[Silver21%](#)

This patient is likely to have *Cryptosporidium parvum* infection. In the immunocompetent, the protozoan causes a self-limiting diarrhoeal illness lasting 7-10 days or may even be asymptomatic. However, in this case there is likely to be co-existing immunosuppression from

human immunodeficiency virus infection, which can result in a severe cholera-like diarrhoea syndrome. The most appropriate staining technique in this case is a modified acid-fast stain such as Ziehl-Neelson, which will stain *C. parvum* oocysts red. Periodic acid-schiff is used on jejunal biopsy specimens to diagnose Whipples disease. Silver staining can pick up *Pneumocystis jiroveci* on sputum samples. Sudan stain is used to diagnose steatorrhoea, and Romanowsky is a blood staining method which preceded Giemsa staining.

## **HIV: diarrhoea**

Diarrhoea is common in patients with HIV. This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections

Possible causes

- Cryptosporidium + other protozoa (most common)
- Cytomegalovirus
- *Mycobacterium avium intracellulare*
- Giardia

Cryptosporidium is the most common infective cause of diarrhoea in HIV patients. It is an intracellular protozoa and has an incubation period of 7 days. Presentation is very variable, ranging from mild to severe diarrhoea. A modified Ziehl-Neelsen stain (acid-fast stain) of the stool may reveal the characteristic red cysts of Cryptosporidium. Treatment is difficult, with the mainstay of management being supportive therapy\*

*Mycobacterium avium intracellulare* is an atypical mycobacteria seen with the CD4 count is below 50. Typical features include fever, sweats, abdominal pain and diarrhoea. There may be hepatomegaly and deranged LFTs. Diagnosis is made by blood cultures and bone marrow examination. Management is with rifabutin, ethambutol and clarithromycin

\*nitazoxanide is licensed in the US for immunocompetent patients

## **Question 10 of 173**

A 26-year-old woman attends the emergency department requesting treatment following being scratched by a cat two days previously. She had been on holiday with family in Sri Lanka and had been playing with an apparently normal cat who came up to her in the street. Unfortunately, the cat had then scratched her on the forearm and hand, although she insisted that her wounds

had only been superficial with no bleeding or broken skin. A relative (a doctor at the local hospital) had subsequently caught the cat and has been holding it in quarantine at his home. The patient had then returned to the UK so as to not miss her flight but on the advice of her relative was requesting treatment for a possible rabies exposure.

The patient's past medical history was significant only for tibial plateau fracture sustained in a sporting accident five years previously. She did not take any regular medications and denied any allergies. She did not recall ever having had a previous course of rabies vaccination.

Examination of the patient demonstrated multiple superficial scratches to her left arm that appeared to be healing normally. There were no areas of broken skin or areas consistent with bite marks. The patient was fully oriented with normal cranial nerve and peripheral nervous examinations. Basic observations were within physiological limits.

What is the correct rabies post-exposure prophylaxis for this patient?

[No action required 23% Full course rabies vaccination 15% Full course rabies vaccination, stopped if quarantined cat is healthy 10 days after exposure 25% Full course rabies vaccination and rabies immunoglobulin 25% Full course rabies vaccination if quarantined cat shows signs of rabies within 10 days of exposure 12%](#)

Sri Lanka is a high risk area for rabies so incidents such as the one described above must be treated with caution. Common animal vectors include dogs, cats, ferrets and bats. The exposure described above would be considered category II with minor scratches and abrasions only and no areas of broken skin. In addition, in this case the animal in question has been held in quarantine by a reliable observer.

WHO recommendations for such an event in a patient without a history of rabies vaccination would be to commence full course vaccination immediately, but to stop vaccination schedule if the cat remains healthy after observation for 10 days. Administration of rabies immunoglobulin is recommended only for category III exposures involving transdermal bites or scratches or any exposures involving bats.

In an individual with a history of previous rabies vaccination, a short course vaccination schedule may be followed.

Given the long incubation time of rabies (in one study the median was 80 days) it is falsely reassuring that the patient is currently well with no neurological signs and symptoms. Indeed, following onset of the acute neurological phase of rabies there is no benefit from providing post-exposure prophylaxis.

Crowcroft N, Thampi N. The prevention and management of rabies. BMJ 2015;350:g7827.

## Rabies

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus (specifically a lyssavirus) and has a bullet-shaped capsid. The vast majority of cases are caused by dog bites but it may also be transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Rabies is estimated to still kill around 25,000-50,000 people across the world each year. The vast majority of the disease burden falls on people in poor rural areas of Africa and Asia. Children are particularly at risk.

### Features

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at-risk countries:

- the wound should be washed
- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination. If possible, the dose should be administered locally around the wound

If untreated the disease is nearly always fatal.

### Question 1 of 163

A 38-year-old male presented to the Emergency Department complaining of feeling unwell. He complained of a headache that had been present for the last two days which he described a continuous ache worse in the morning, as well as a sore throat. He later developed diarrhoea, opening his bowels three times per day passing watery loose stool. Since then he has deteriorated, complaining of nausea and vomiting on the day of admission. He also noted a new rash on his chest which developed over the last few hours and complained of pains in his muscles. He had returned two weeks ago from a six-month backpacking expedition around

Africa and Far East Asia; he was prescribed doxycycline as antimalarial prophylaxis but had discontinued them two weeks into his trip after suffering from severe sunburns. He had not taken recommended vaccinations prior to his trip as he was engaged with work commitments. His past medical history comprised of asthma and depression for which he was prescribed sertraline 100mg OD and Clenil modulite 2 puffs BD.

Examination revealed the presence of an unwell gentleman. His temperature was 40.1°C, heart rate 122 bpm, respiratory rate 22/min, oxygen saturations 95% on air and he had a blood pressure of 94/68 mmHg. He had a plethoric facial appearance, and multiple petechiae were noted on his chest and face. Examination of his cardiovascular system revealed the presence of normal heart sounds with a JVP of 2cm and a bounding radial pulse and vasodilated peripheries. Examination of his respiratory system revealed tachypnoea but with vesicular breath sounds. Examination of the gastrointestinal and neurological systems was unremarkable, with no neck stiffness, negative Kernig's and Brudzinski's signs. His GCS was 15. Multiple insect bites were noted on his legs and arms.

He was promptly transferred to the resuscitation area where two large bore cannulae were inserted and aggressive intravenous fluid resuscitation was commenced. A urinary catheter was inserted. The doctor inserting the cannulae noted that the sites of venepuncture continued to ooze despite the application of continual mechanical pressure.

Initial investigations revealed the following results:

Hb	102 g/l
Platelets	$8 \times 10^9/l$
WBC	$3.2 \times 10^9/l$
Neutrophils	$2.2 \times 10^9/l$
Lymphocytes	$0.8 \times 10^9/l$
Monocytes	$0.1 \times 10^9/l$
Eosinophils	$0.1 \times 10^9/l$
ESR	48 mm/hr
PTT	17 (NR 12-14s)
APTT	53 (NR 30-46s)
Fibrinogen	0.6 (NR 2-4g/l)
D-Dimer	428 (NR <230ng/ml)
Na <sup>+</sup>	130 mmol/l
K <sup>+</sup>	6.2 mmol/l
Urea	18.1 mmol/l
Creatinine	262 $\mu$ mol/l
CRP	96 mg/l

Bilirubin 28 µmol/l  
ALP 162 u/l  
ALT 122 u/l  
Total protein 52 g/l  
Albumin 22 g/l

Blood MCS x3: awaiting result  
Urine MCS: awaiting result  
Thick film: negative  
Thin film: awaiting result

Portable chest x-ray: normal appearance of heart and lung fields  
ECG: sinus tachycardia 122bpm  
Urinalysis: trace protein, ketones ++, nil else

What is the most likely diagnosis?

[Viral haemorrhagic fever 56% Malaria 12% Typhus 7% Thrombotic thrombocytopenic purpura 12% Typhoid fever 13%](#)

The Viral Haemorrhagic Fevers describe infection by a group of RNA viruses which include Yellow fever, Lassa fever and Ebola virus. Given the current outbreak in West Africa, this group of infections must be considered as a differential in returning travellers presenting with a fever. They are characterised by initially non-specific symptoms such as fever, headache, vomiting, sore throat, diarrhoea and myalgic muscle pains, progressing to shock, renal failure and the presence of disseminated intravascular coagulation (DIC). Investigations characteristically reveal an anaemia with thrombocytopenia, low lymphocyte count, deranged liver function and the presence of DIC. This condition requires intensive supportive care and early diagnosis is imperative. There are of course many differentials, malaria being a key one here, but the absence of parasites on thick film make this a less likely diagnosis.

## **Viral haemorrhagic fever**

Examples of viral haemorrhagic fever include:

- Flaviviridae: dengue, yellow fever
- Arenaviridae: Lassa fever
- Filoviridae: Ebola virus



Question 2 of 163

A 35-year-old man is reviewed in respiratory clinic with symptoms of a chronic cough with occasional haemoptysis, night sweats and significant unintentional weight loss. The patient is originally from the Russian Federation and on direct questioning through an interpreter discloses that he had spent five years in a Moscow prison for drugs offences. Aside from a period of alcohol abuse in his early twenties, the patient denies any other medical history and takes no medications. He currently is living in shared accommodation and works on a building site, although he is struggling to continue to work due to his current illness.

General inspection showed the patient to be cachexic with tobacco stained fingernails. Auscultation of the chest revealed some reduced air entry in the upper zones bilaterally. There was palpable lymphadenopathy in the anterior cervical chain.

Please see results of investigations below.

Chest x-ray: patchy shadowing in both upper lobes with evidence of cavity formation on the right side; no pneumothorax; normal mediastinal shadow.

Sputum microscopy: acid fast bacilli

Phenotypic indirect drug susceptibility testing: rifampicin (resistant); ofloxacin (sensitive); moxifloxacin (sensitive); isoniazid (resistant); amikacin (sensitive); capreomycin (sensitive).

What is the most appropriate treatment regime for this patient?

[Combination therapy with 5 drugs for 24-36 months8%](#)[Combination therapy with 5 drugs for 18-24 months41%](#)[Combination therapy with 4 drugs for 24-36 months7%](#)[Combination therapy with 4 drugs for 12 months24%](#)[Combination therapy with 4 drugs for 18-24 months21%](#)

The patient presents with a typical history for active pulmonary tuberculosis. His history of incarceration in a prison in the Russian Federation makes him at high risk of having contracted a multi-drug resistant strain of TB. Microbiology results confirm resistance to rifampicin and isoniazid consistent with multi-drug resistance, however without resistance to any fluoroquinolone or second line injectable agents that would suggest extensively drug resistant TB.

Recommended treatment for multi-drug resistant TB requires 18-24 months of at least 5 drugs. Depending on the microbiological testing services available, the regime may be individualised to an individual patients infection or based on a standardised regime based on local resistance patterns.

Millard J, Ugarte-Gil C, Moore D. Multidrug resistant tuberculosis. BMJ 2015;350:h882.

## Tuberculosis: management

Stop medication if LFT's > 5 times normal limit

Immune reconstitution disease

- occurs typically 3-6 weeks after starting treatment
- often presents with enlarging lymph nodes

Question 1 of 161

As the medical registrar on-call you are called to see a 25-year-old male in the Emergency Department (ED). The young male presented to the ED with a fever and productive cough of green sputum. When you arrive he looks unwell and although alert is a difficult historian.

Concerned, you immediately assess him from head to toe:

Airway     Airway patient, able to speak in sentences

Breathing     Sats 90% on room air, Resp Rate 25 / min, coarse creps bilaterally on auscultation

Circulation     Heart rate 110 beats per minute, blood pressure 90/55 mm/Hg

Disability     Glasgow coma scale 15/15, capillary blood glucose 5.5

Exposure     Multiple boils noted distributed widely across the patient's body

You inquire about the history of the boils identified on examination. The patient is unsure how long he has had them for, however, mentions that two of his family members recently were prescribed antibiotics by their family GP for similar lesions.

You start the patient on high flow oxygen, gain IV access taking blood cultures and give a fluid bolus. An urgent portable chest X-ray is requested which appears to show bilateral consolidation with multiple cavitating lesions.

What is the most likely diagnosis

[Streptococcal infection 9%](#) [PVL-producing staphylococcal infection 66%](#) [Tuberculosis 7%](#) [Fungal chest infection 6%](#) [Klebsiella infection 12%](#)

Panton-Valentine Leukocidin is a pore-forming toxin which is produced by staphylococcus aureus. It has an affinity for white blood cells and the endothelium. Clinically PVL will often

present with a necrotising pneumonia, characterised by severe bilateral pneumonia with cavitations on X-ray. Often patients presenting will have a history of boils or necrotic skin lesions. As the staphylococcus is easily transmitted there may be a recent family history of similar infections / boils.

Although all of the answers in this stem could be associated with cavitating pneumonia, the severity of the clinical presentation and history of boils in the family points towards a PVL-pneumonia.

## **Staphylococci**

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease. Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase

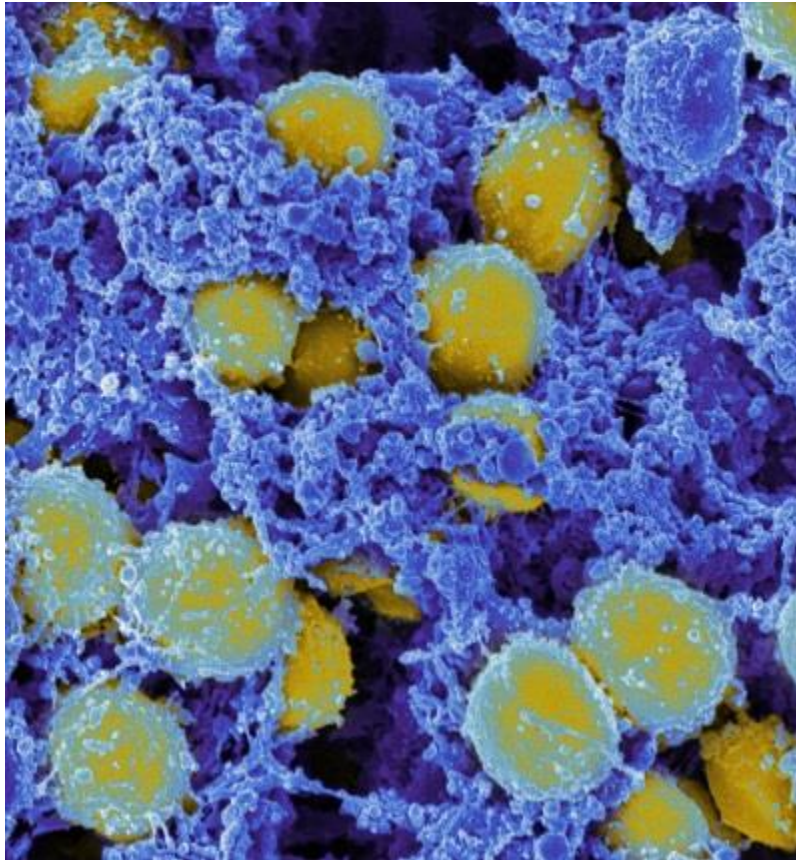
The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

### ***Staphylococcus aureus***

- Coagulase-positive
- Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome

### ***Staphylococcus epidermidis***

- Coagulase-negative
- Cause of central line infections and infective endocarditis



Scanning electromicrograph of Staphylococcus aureus bacteria. Credit: NIAID

#### Question 2 of 161

A 30-year-old male refugee presents with fever, rigours and right flank pain. With the help of a translator you discover he has been unwell for 7 days with these symptoms that are getting progressively worse. He says he is otherwise fit and well and does not take any regular medications. He moved to the UK 2 months ago having lived his entire life in Sudan.

On examination he has a temperature of 38.2 degrees, a heart rate of 98 beats per minute, a blood pressure of 110/70 and a respiratory rate of 20. He is lying calmly in the bed but is tender over the renal angle on the right side.

#### Investigations:

serum sodium	138 mmol/L (137-144)
serum potassium	5.5 mmol/L (3.5-4.9)
serum creatinine	240 mol/L (60-110)

haemoglobin	98 g/L (130-180)
white cell count	$15.4 \times 10^9/\text{L}$ (4.0-11.0)
eosinophil count	$0.89 \times 10^9/\text{L}$ (0.04-0.40)
platelet count	$378 \times 10^9/\text{L}$ (150-400)
urine microscopy	red cells 2+, white cells 3+, protein 2+
ultrasound scan of abdomen	right sided hydronephrosis and hydroureter, fibrotic and calcified bladder

What is the most likely underlying diagnosis?

[Schistosomiasis japonicum 6%](#)[Chronic vesico-ureteric reflux and secondary pyelonephritis 6%](#)[Squamous cell carcinoma of the bladder 5%](#)[Schistosomiasis haematobium 68%](#)[Schistosomiasis mansoni 15%](#)

The clinical picture here is of an acute pyelonephritis with fever, rigours and tenderness over the renal angle. However blood analysis and imaging suggest there is another entity at play that has predisposed the patient to this.

*S. mansoni* and *S. japonicum*, *S. mekongi* and *S. intercalatum* produce eggs that can invade the bowel wall causing an intense inflammatory reaction that gives rise to loose bloody stools. Eggs can also migrate to liver through the portal venous system where they can elicit a granulomatous fibrosing reaction. This can eventually lead to the blockade of venous blood and flow. Portal venous hypertension results which can give rise to varices and upper gastrointestinal bleeding.

*S. haematobium* on the other hand leads to granulomatous inflammation, ulceration of the vesicle and ureteral walls. Subsequent fibrosis can cause bladder neck obstruction, hydroureter and hydronephrosis. These changes can cause a chronic renal impairment and predispose to secondary bacterial infection as well as squamous cell carcinoma.

In addition, all schistosome species can result in immune complex deposition in the kidneys leading to a proteinuria and nephrotic syndrome.

## Schistosomiasis

Schistosomiasis, or bilharzia, is a parasitic flatworm infection. The following types of schistosomiasis are recognised:

- *Schistosoma mansoni* and *Schistosoma intercalatum*: intestinal schistosomiasis
- *Schistosoma haematobium*: urinary schistosomiasis

### **Schistosoma haematobium**

This typically presents as a 'swimmer's itch' in patients who have recently returned from Africa. *Schistosoma haematobium* is a risk factor for squamous cell bladder cancer

#### Features

- frequency
- haematuria
- bladder calcification

#### Management

- single oral dose of praziquantel

#### Question 3 of 161

A 43-year-old gentleman presents with bloody diarrhoea. He is HIV positive and has a CD4 count of 150 cells/ $\mu$ L.

He had been on a trip to Zimbabwe 10 months previously. Over the past 2 weeks, he had symptoms of anorexia and mild abdominal discomfort. These had progressed on to severe abdominal cramps and bloody diarrhoea.

He has a temperature of 37.8°C, a blood pressure of 100/60 and a pulse of 111/min. On examination, he looks unwell, is emaciated and has generalised tenderness on examination of his abdomen. There is no guarding or peritonitis.

What is the most likely causative organism?

[\*Giardia lamblia\*13%\*Toxoplasma gondii\*7%\*Entamoeba histolytica\*37%\*Cytomegalovirus\*33%\*Strongyloides stercoralis\*10%](#)

*Entamoeba histolytica* is the only pathogen here which typically causes bloody diarrhoea in an immunocompromised individual and hence is the correct answer. *Giardia* typically causes steatorrhea, *Toxoplasma gondii* is more likely to cause a central nervous system infection, and

while CMV can cause diarrhoea it is rarely a presenting feature of the infection. While *Strongyloides stercoralis* can cause diarrhoea, it is usually watery rather than bloody.

## Amoebiasis

Amoebiasis is caused by *Entamoeba histolytica* (an amoeboid protozoan) and spread by the faecal-oral route. It is estimated that 10% of the world's population is chronically infected. Infection can be asymptomatic, cause mild diarrhoea or severe amoebic dysentery. Amoebiasis also causes liver and colonic abscesses

### Amoebic dysentery

- profuse, bloody diarrhoea
- stool microscopy may show trophozoites
- treatment is with metronidazole

### Amoebic liver abscess

- usually a single mass in the right lobe (may be multiple)
- features: fever, RUQ pain
- serology is positive in > 90%

## Question 1 of 158

A 45-year-old female presents to your clinic with bilateral lower limb lesions. She said that it initially started as a small nodule on the right shin which then broke down into an exudative ulcer. Over the past year she has developed widespread 'cauliflower-like' lesions over her whole body. On examination you note a painless ulcer with scab over the anterior right shin, and generalised papillomas over the face, trunk, genitalia and buttocks.

Investigations demonstrate:

TPHA (Treponema pallidum Haem Agglutination test) Positive

What is the most likely diagnosis?

[Pinta 1% Syphilis 33% Yaws 34% Pyoderma gangrenosum 9% Kaposi's sarcoma 12%](#)

Treponemal specific antibody tests (e.g. TPHA) are very specific to *Treponema* but not necessarily syphilis, as the species *Treponema* can cause a variety of diseases including syphilis, yaws and pinta

Care must be taken when interpreting syphilis investigations. Cardiolipin tests (e.g. VDRL and RPR) are non-specific and can be positive in many diseases such as TB, malaria and HIV.

Treponemal specific antibody tests (e.g. TPHA) are very specific to *Treponema*, however the species *Treponema* can cause a variety of diseases including syphilis, yaws and pinta.

Yaws is a chronic infection that affects mainly the skin, bone and cartilage. The disease occurs mainly in low socio-economic communities in tropical areas of Africa, Asia and Latin America. The causative organism is a bacterium called *Treponema pertenue*, a subspecies of *Treponema pallidum* that causes venereal syphilis. However, yaws is a non-venereal infection.

In primary yaws, a single skin lesion develops at the point of entry of the bacterium after 2-4 weeks. This nodule can break down into an exudative ulcer. Without treatment, secondary yaws can occur, resulting in multiple lesions appear all over the body, more commonly over the face, trunk, genitalia and buttocks. Later on in the disease course, widespread bone, joint and soft tissue destruction can occur.

## **Syphilis: investigation**

*Treponema pallidum* is a very sensitive organism and cannot be grown on artificial media. The diagnosis is therefore usually based on clinical features, serology and microscopic examination of infected tissue

Serological tests can be divided into

- cardiolipin tests (not treponeme specific)
- treponemal specific antibody tests

Cardiolipin tests

- syphilis infection leads to the production of non-specific antibodies that react to cardiolipin
- examples include VDRL (Venereal Disease Research Laboratory) & RPR (rapid plasma reagin)
- insensitive in late syphilis
- becomes negative after treatment

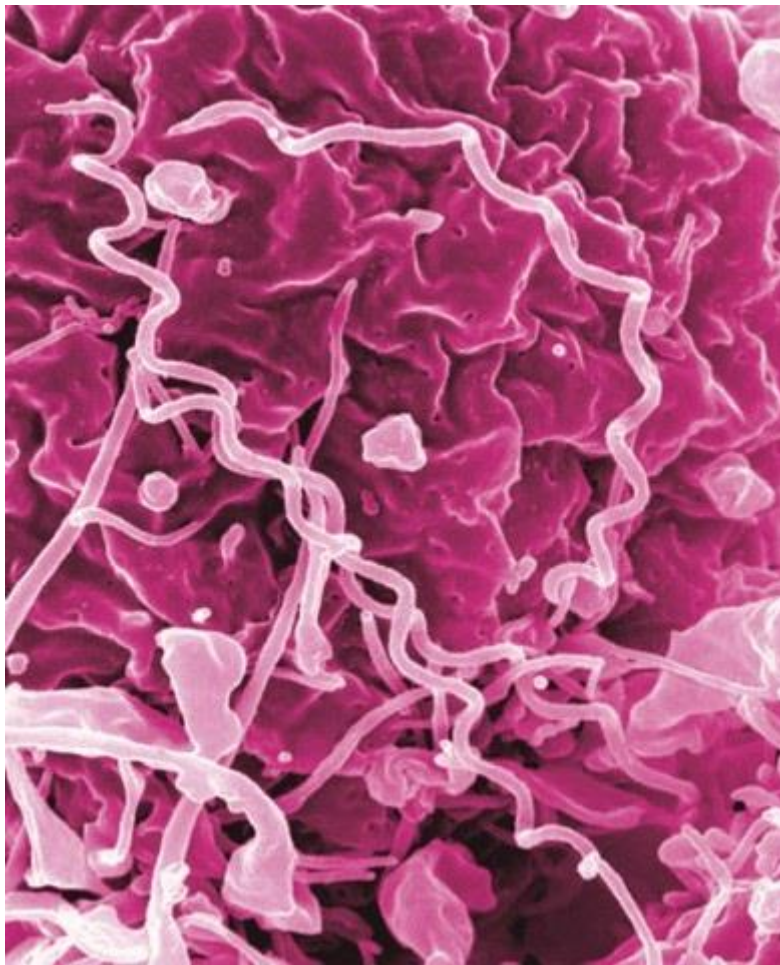


### Treponemal specific antibody tests

- example: TPHA (*Treponema pallidum* HaemAgglutination test)
- remains positive after treatment

### Causes of false positive cardiolipin tests

- pregnancy
- SLE, anti-phospholipid syndrome
- TB
- leprosy
- malaria
- HIV



*Treponema pallidum*, the bacteria that cause syphilis. Note the spiral shape of the organism.  
Credit: NIAID

### Question 2 of 158

A 38 year old man from Nigerian man presents to a gastroenterology clinic. He is a businessman, working for an iron and steel trading company and makes regular trips to Swaziland to visit mining executives.

For the previous four months he has been troubled by diarrhoea, up to 8 episodes a day, with abdominal bloating and cramping. There is no blood visible in the stool. He has previously been treated for tuberculosis as a child.

A stool sample is sent to the lab, and Modified Ziehl-Neelson stain reveals multiple red staining round objects measuring 5 microns in diameter.

What will be the most appropriate treatment?

[Highly active anti-retroviral therapy 33% Co-trimoxazole 14% Rifampicin, isoniazid, ethambutol, pyrazinamide 20% Metronidazole 23% Ciprofloxacin 10%](#)

The diagnosis is cryptosporidium infection. It is the most common cause of chronic diarrhoea in HIV patients. Diagnosis is made by visualisation with modified Zeihl-Neelson stain of stool. You would very rarely expect to see mycobacterium tuberculosis on a faecal sample.

## Cryptosporidiosis

Cryptosporidiosis is the commonest protozoal cause of diarrhoea in the UK. Two species, *Cryptosporidium hominis* and *Cryptosporidium parvum* account for the majority cases.

Cryptosporidiosis is more common in immunocompromised patients (e.g. HIV) and young children.

### Features

- watery diarrhoea
- abdominal cramps
- fever
- in immunocompromised patients the entire gastrointestinal tract may be affected resulting in complications such as sclerosing cholangitis and pancreatitis

### Diagnosis

- stool: modified Ziehl-Neelsen stain (acid-fast stain) of the stool may reveal the characteristic red cysts of *Cryptosporidium*

## Management

- is largely supportive
- nitazoxanide is licensed in the US for immunocompetent patients

## Question 3 of 158

A 19-year-old man returning from Zimbabwe is admitted to the emergency department. He arrived back in the UK one week ago but for the last three days has complained of a severe headache and rigors. He has no significant past medical history. He smokes 10 cigarettes per day and does not drink alcohol.

On examination, the patient is sweaty and appears anxious. Pulse rate is 108/min, blood pressure 91/58 mmHg, temperature 39°C and the respiratory rate 22/min. His chest is clear and heart sounds normal. A brief neurological examination is normal. An urgent blood film reveals malarial parasites. Which of the following would suggest severe malaria infection?

[Blood sugar > 14 mmol/l](#) [12% Bicarbonate < 14 mmol/l](#) [62% CRP > 250 mg/l](#) [6% Temperature > 38.5°C](#) [12% Infection despite use of appropriate antimalarial prophylaxis](#) [9%](#)

The World Health Organisation states that the early recognition and treatment of severe malaria is vital to prevent rapid deterioration in the patient's condition and the onset of life-threatening complications.

Complications indicating severe malaria include:

- hypoglycaemia
- acidosis
- coma
- convulsions
- severe anaemia
- pulmonary oedema

Both coma and convulsions may represent cerebral malaria. In addition the parasite involved and percentage parasitaemia is important in the prognosis and management of malaria

## **Malaria: Falciparum**

### Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 °C
- severe anaemia
- complications as below

### Complications

- cerebral malaria: seizures, coma
- acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
- acute respiratory distress syndrome (ARDS)
- hypoglycaemia
- disseminated intravascular coagulation (DIC)

### Uncomplicated falciparum malaria

- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

### Severe falciparum malaria

- a parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

- Question 4 of 158
- A 36-year-old Somali male presents on the medical take with a severe generalised headache associated with nausea and vomiting. He has been living in the UK for the last 10 years. He was diagnosed with HIV 5 years ago and has been well maintained on therapy with an undetectable viral load and a CD4 count of 500 cells/mm<sup>3</sup>.

He has a long history of headaches since the age of 10 which are normally controlled with simple analgesia. Over the last 2 days he has been suffering with a particularly bad attack which culminated in him becoming aggressive and vomiting profusely. He was noted to have a tonic-clonic seizure whilst in accident and emergency which resolved with diazepam.

Clinical examination reveals a pulse of 78 beats per minute, a blood pressure of 130/90, oxygen saturations of 98% on air and a temperature of 36.8 degrees. There was no focal neurological defects.

A CT scan subsequently showed cystic and calcified lesions within the brain and mild hydrocephalus.

What is the most likely diagnosis?

- [Tuberculous meningitis7%](#)[Cryptococcal meningitis12%](#)[Lymphoma7%](#)[Neurocysticercosis67%](#)[Human african trypanosomiasis7%](#)
- 

Cysticercosis is caused by the larval stage of the tapeworm *Taenia solium*. Clinical syndromes that can arise include neurocysticercosis (NCC) and extraneural cysticercosis. In endemic areas NCC is an important cause of adult-onset seizures.

Cysticercosis is transmitted by ingestion of *T. solium* eggs shed in the stool of a human tapeworm carrier. Following ingestion, embryos (oncospheres) hatch in the small intestine, invade the bowel wall and disseminate hematogenously to the brain, muscle, liver and other tissues. Cysts located in the brain result in neurocysticercosis and can lead to hydrocephalus if they obstruct the outflow of CSF from the ventricles. The condition can be chronic and develop over a protracted period of time.

This question relies primarily on knowledge of the relevant condition and your ability to think beyond the fact that the patient has HIV. While the other options are all plausible you are given clues throughout the question on which you can discount each one until you are left with the correct answer.

The first hint is that his HIV was diagnosed early and is very well controlled. This makes an opportunistic infection incredibly unlikely therefore discounting cryptococcosis and TB meningitis. There are two forms of human african trypanosomiasis both transmitted by the tsetse fly, *T.gambiense* a chronic condition contracted in west africa and

T.rhodiesiense that is acutely progressive and contracted in east africa. Given that he has been in the UK for 5 years we can discount T.rhodiesiense and the finding of calcified lesions on the CT would be most unusual for T.gambiense.

This leaves us with lymphoma and neurocystercosis, lymphoma will generally present with progressive focal neurology over a period of time and is unlikely to show calcified lesions in the brain.

- 

- **Helminths**

- 

**Nematodes (roundworms)**

Worm	Notes	Treatment
	Larvae are present in soil and gain access to the body by penetrating the skin	
<i>Strongyloides stercoralis</i>	Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms	Ivermectin and -bendazoles are used
<i>Enterobius vermicularis</i> (pinworm)	Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	-bendazoles
<i>Ancylostoma duodenale, Necator americanus</i> (hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova Transmission by deer fly and mango fly	-bendazoles
<i>Loa loa</i>	Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae	Diethylcarbamazine
<i>Trichinella spiralis</i>	Typically develops after eating raw pork	-bendazoles

Worm	Notes	Treatment
<i>Onchocerca volvulus</i>	Features include fever, periorbital oedema and myositis (larvae encyst in muscle) Causes 'river blindness'. Spread by female blackflies	Ivermectin rIVERblindness = IVERmectin
<i>Wuchereria bancrofti</i>	Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria Transmission by female mosquito Causes blockage of lymphatics → elephantiasis Transmitted through ingestion of infective eggs.	Diethylcarbamazine
<i>Toxocara canis</i> (dog roundworm)	Features include visceral larva migrans and retinal granulomas VISCious dogs → blindness Eggs are visible in faeces	Diethylcarbamazine
<i>Ascaris lumbricoides</i> (giant roundworm)	May cause intestinal obstruction and occasional migrate to lung (Löffler's syndrome)	-bendazoles

•

### Cestodes (tapeworms)

Worm	Notes	Treatment
<i>Echinococcus granulosus</i>	Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers.	-bendazoles
<i>Taenia solium</i>	Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal) Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
<i>Fasciola hepatica</i> (the liver fluke)	May cause biliary obstruction	Triclabendazole

•

### Trematodes (flukes)

Worm	Notes	Treatment
<i>Schistosoma haematobium</i>	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel

Worm	Notes	Treatment
<i>Paragonimus westermani</i>	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs Caused by undercooked fish	Praziquantel
<i>Clonorchis sinensis</i>	Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	

#### Question 5 of 158

You see Mr Smith, a 35-year-old man-who-has-sex-with-men (MSM) in clinic. He was diagnosed with HIV 5 years ago, commencing combination antiretroviral therapy (cART). Following a number of alterations to his cART due to side effects he responded well to a combination of tenofovir, emtricitabine and ritonavir boosted atazanavir. His plasma viral load (pVL) of HIV RNA has remained undetectable and his adherence has been good.

In clinic today Mr Smith reports 5 weeks of drenching night sweats, a dry cough and some subjective weight loss, going up a belt buckle during this time period. On examination you note that he appears pale and auscultation of the chest elicits crepitations in the left upper zone. Your perform a chest X-ray which demonstrates a cavitating lesion in the left upper lobe. You arrange induced sputum samples which confirm a diagnosis of pulmonary tuberculosis.

You explain your diagnosis to Mr Smith and the need to urgently commence him on anti-tuberculosis chemotherapy. Whilst he is happy to commence treatment, he is adamant that he does not want to risk his viral control and states that he is not willing to consider altering his cART regime at present.

What is the most appropriate management step to treat Mr Smith?

[Hold his ART6%Commence rifabutin, isoniazid, ethambutol and pyrazinamide45%Commence isoniazid monotherapy7%Switch protease inhibitor to an novel ARV agent15%Commence rifampicin, isoniazid, pyrazinamide and ethambutol27%](#)

The correct answer for this scenario is to commence rifabutin, isoniazid, ethambutol and pyrazinamide.

This scenario tests your knowledge of rifamycins in the treatment of tuberculosis. Rifamycin containing anti-tuberculosis chemotherapy regimes are superior to those which do not contain a rifamycin agent. However, in this scenario the patient is also taking taking a protease inhibitor as part of their antiretroviral therapy.



Rifampicin, the common rifamycin agent in anti-tuberculosis regimes, is a potent inducer of liver enzymes, such as cytochrome P450. Furthermore, it up-regulates the expression of P-glycoprotein in the gastrointestinal tract. This leads to reduced absorption and increased metabolism of certain medications, protease inhibitors being one of these (ritonavir booster atazanavir). Co-administration of a protease inhibitor with rifampicin therefore will often lead to subtherapeutic levels of the protease inhibitor.

In this scenario, the patient is stable on his current antiretroviral treatment and not keen to switch at present. Therefore, the British HIV Association (BHIVA) suggest the substitution of rifampicin for an alternative rifamycin agent (rifabutin or rifapentine), which has less inducing action of cytochrome P450 and therefore allows the patient to continue their current HIV treatment regime. Regimes containing rifabutin (dose 150mg three times a week) have been shown to have equivocal in outcomes of treatment in the few small observational studies performed in patients with HIV/TB co-infection.

## **Tuberculosis: management**

Stop medication if LFT's > 5 times normal limit

Immune reconstitution disease

- occurs typically 3-6 weeks after starting treatment
- often presents with enlarging lymph nodes

### Question 1 of 151

A 50-year-old man presents to the Emergency Department after becoming increasingly unwell over the previous two weeks. His initial symptoms were fevers increasing shortness of breath. In the last 24 hours he had experienced several episodes of haemoptysis and bloody diarrhoea precipitating his attendance to hospital.

Past medical history included a diagnosis of systemic lupus erythematosus five years previously. This disease had been poorly controlled in recent months requiring the patient to take prednisolone 40 mg daily and hydroxychloroquine 400 mg daily. The patient was originally from Mali and had emigrated to the UK twenty years previously. He had returned to visit family in Africa earlier in the year and had not taken malaria prophylaxis whilst abroad.

Initial assessment revealed the patient to be very unwell. Respiratory rate was 32 with O<sub>2</sub> saturations of 94 % on high flow oxygen. Blood pressure was 80/50 mmHg with no improvement in hypotension following aggressive fluid resuscitation. The patient was intubated and ventilated and transferred to the Intensive Care Unit for inotropic support.

Results of immediate investigations are listed below.

Chest x-ray: widespread diffuse pulmonary infiltrates; left sided pleural effusion; no free air under the diaphragm

Abdominal x-ray: multiple loops of distended small bowel; no evidence of free air

Hb	11.2 g/dl
Mean cell volume	83 fL
Platelets	$150 \times 10^9/l$
WBC	$18.7 \times 10^9/l$
Neutrophils	$14.8 \times 10^9/l$
Lymphocytes	$2.0 \times 10^9/l$
Monocytes	$1.0 \times 10^9/l$
Eosinophils	$0.9 \times 10^9/l$
Blood film	no abnormality detected
Internationalised normalised ratio	1.2

Na <sup>+</sup>	124 mmol/l
K <sup>+</sup>	4.9 mmol/l
Urea	15 mmol/l
Creatinine	190 $\mu$ mol/l
C-reactive protein	284 mg/dL

Blood cultures: Gram negative cocci (positive after 24 hours)

Pleural fluid microscopy: filariform larvae

What is the most likely underlying diagnosis?

[Caecal carcinoma4%Strongyloides hyperinfection syndrome76%Churg-Strauss vasculitis5%Plasmodium falciparum infection8%Disseminated haematogenous tuberculosis7%](#)

Strongyloides hyperinfection syndrome occurs in immunosuppressed individuals with coexistent Strongyloides stercoralis infection. Uncontrolled proliferation of larvae occurs with dissemination to end organs.

As in this individual, systemic sepsis often occurs due to involvement of the gut wall allowing translocation of gut bacteria. Other features include pulmonary infiltrates, paralytic ileus, gastrointestinal bleeding and syndrome of inappropriate ADH secretion.

Filariform larvae can be found in body fluids by microscopy and it is this that confirms the

diagnosis in this case. Due to immunosuppression, eosinophilia is often absent. Given the patient's country of origin, strongyloidosis is most likely to have been chronic, but could have been acquired on his recent trip to Africa.

*Plasmodium falciparum* infection can cause a similar presentation, although the normal blood film in this case makes this unlikely. Severe tuberculosis infection tends to predominantly involve the lungs with a varying degree of involvement of other organ systems.

Churg-Strauss vasculitis can cause severe abdominal symptoms including infarction and perforation. However, the normal eosinophil count, short history and immunosuppression do not support this diagnosis.

Colonic carcinoma can lead to translocation of gut bacteria and gram-negative sepsis. However, this diagnosis would not explain all of the findings in this case and is not supported by the normal mean cell volume.

### ***Strongyloides stercoralis***

*Strongyloides stercoralis* is a human parasitic nematode worm. The larvae are present in soil and gain access to the body by penetrating the skin. Infection with *Strongyloides stercoralis* causes strongyloidiasis.

#### Features

- diarrhoea
- abdominal pain/bloating
- papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

#### Treatment

- ivermectin and albendazole are used

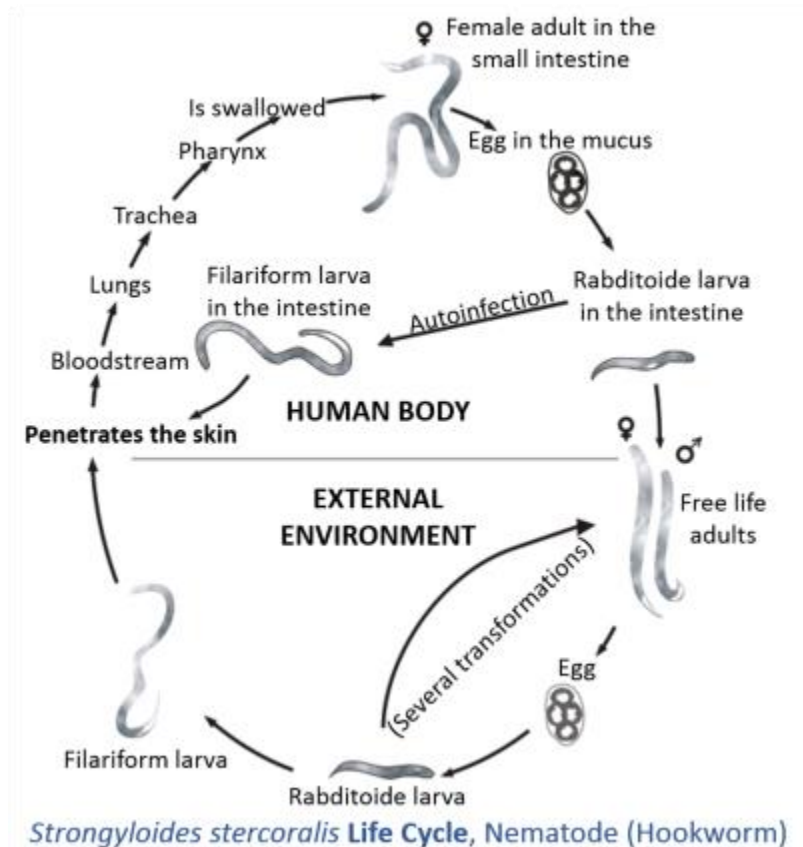


Image sourced from [Wikipedia](#)

Diagram showing the lifecycle of *Strongyloides stercoralis*

Question 2 of 151

A 25-year-old man presents feverish with a productive cough. He is reluctant to tell you about himself. On examination, he has bronchial breathing at both bases. He has normal heart sounds. His observations show a respiratory rate of 24/min, oxygen saturations of 94% on room air, a temperature of 38 degrees celsius, heart rate of 98/min, blood pressure 100/64mmHg. There are track marks on his arms. Which organism is responsible?

[Staphylococcus aureus](#)50%[Streptococcus pneumoniae](#)9%[Klebsiella pneumoniae](#)14%[Pneumocystis jirovecii](#)16%[Mycoplasma pneumoniae](#)11%

*Staphylococcus aureus* is an organism often found on the skin. It is therefore commonly associated with systemic infections in intravenous drug users. This is hinted here by the presence of track marks. It also causes bibasal pneumonia as opposed to *Streptococcus pneumoniae* that is the most common cause of a single lobar pneumonia.

## Staphylococci

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease. Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase

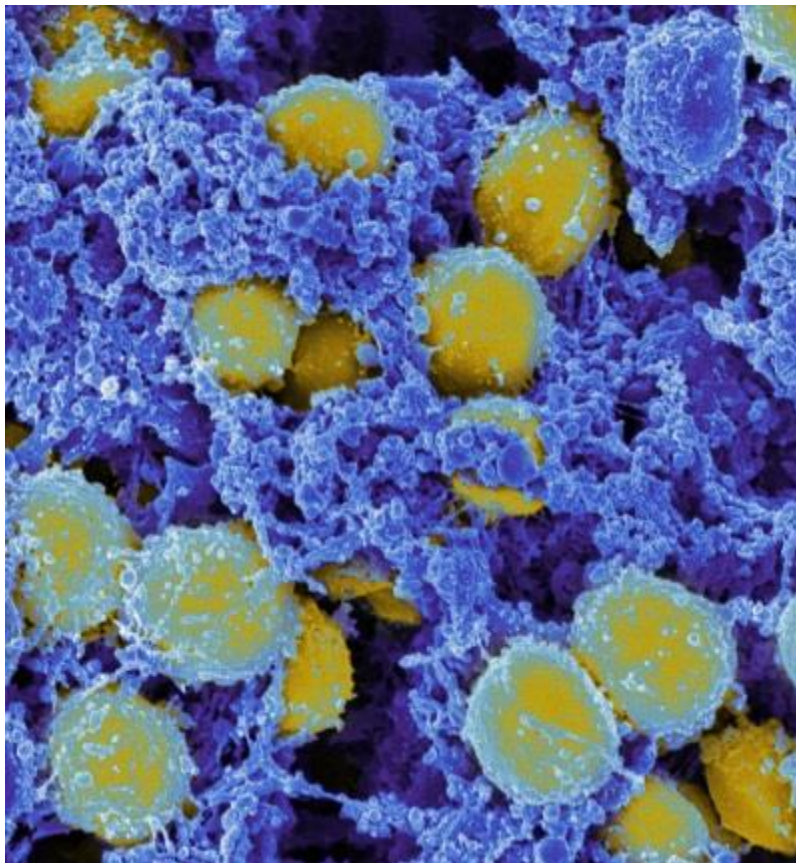
The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

### *Staphylococcus aureus*

- Coagulase-positive
- Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome

### *Staphylococcus epidermidis*

- Coagulase-negative
- Cause of central line infections and infective endocarditis





Scanning electromicrograph of Staphylococcus aureus bacteria. Credit: NIAID

### Question 3 of 151

A 27 year-old Lithuanian male presents to the Emergency Department with a short history productive cough, fever and breathlessness. The chest X-Ray shows left upper zone consolidation. His white cell count and CRP are elevated and IV antibiotics are commenced for a community acquired pneumonia. He makes some improvement after 48 hours but remains on 4L of oxygen to maintain adequate saturations. An interferon gamma release assay for mycobacterium is positive.

What would be the correct course of action?

[Send three morning sputum samples for acid fast bacilli44%](#) [Arrange a bronchoscopy and washings for acid fast bacilli14%](#) [No action, continue antibiotics, repeat CXR in 6 weeks time6%](#) [Treat for latent pulmonary tuberculosis with two agents11%](#) [Treat for active pulmonary tuberculosis with quadruple therapy26%](#)

This young gentleman's positive interferon release assay shows he has been exposed to tuberculosis in the past. It however does not give any information regarding this active infection which could represent pulmonary tuberculosis or bacterial pneumonia. A wise course of action would include isolating the patient and sending three morning sputum samples to look for acid fast bacilli. He is not currently fit for bronchoscopy given his oxygen requirements.

## **Tuberculosis: screening**

The Mantoux test is the main technique used to screen for latent tuberculosis. In recent years the interferon-gamma blood test has also been introduced. It is used in a number of specific situations such as:

- the Mantoux test is positive or equivocal
- people where a tuberculin test may be falsely negative (see below)

## **Mantoux test**

- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected intradermally

- result read 2-3 days later

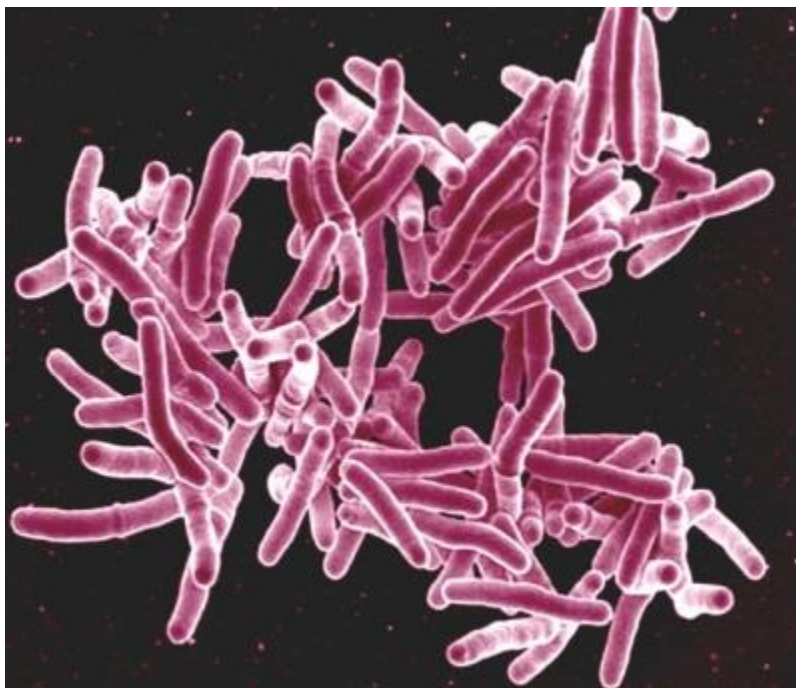
<b>Diameter of induration</b>	<b>Positivity</b>	<b>Interpretation</b>
< 6mm	Negative - no significant hypersensitivity to tuberculin protein	Previously unvaccinated individuals may be given the BCG
6 - 15mm	Positive - hypersensitive to tuberculin protein	Should not be given BCG. May be due to previous TB infection or BCG
> 15mm	Strongly positive - strongly hypersensitive to tuberculin protein	Suggests tuberculosis infection.

False negative tests may be caused by:

- miliary TB
- sarcoidosis
- HIV
- lymphoma
- very young age (e.g. < 6 months)

### **Heaf test**

The Heaf test was previously used in the UK but has been since been discontinued. It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.





Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause TB. Credit: NIAID

#### Question 4 of 151

A 67-year-old woman is referred to the Emergency department by her GP because of an acute rise in serum creatinine. She has a history of Type 2 diabetes and takes lisinopril, amlodipine and indapamide as well as metformin and simvastatin, and has recently been prescribed trimethoprim for a UTI. Her blood pressure is 148/84 mmHg, with no postural drop on standing. There are no signs of fluid overload.

Na <sup>+</sup>	140 mmol/l
K <sup>+</sup>	4.9 mmol/l
Urea	5.8 mmol/l
Creatinine	162 µmol/l
Creatinine (one month earlier)	112 µmol/l

Which of the following is the most likely cause of her creatinine elevation?

[Amlodipine4%](#)[Lisinopril11%](#)[Post-renal failure5%](#)[Pre-renal failure6%](#)[Trimethoprim75%](#)

Trimethoprim is associated with a reversible elevation in serum creatinine because of a reduction in tubular excretion. Creatinine returns to normal once therapy ceases, and there is no effect on the GFR.

There is no suggestion of postural drop on blood pressure testing to support either pre-renal failure or amlodipine being the likely cause of creatinine elevation, and it's likely that the lisinopril has been prescribed for a prolonged period, rather than it being the cause of an acute rise in creatinine due to renal artery stenosis.

There are no symptoms of urinary obstruction to suggest post-renal failure.

### Trimethoprim

Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.



## Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase

## Adverse effects

- myelosuppression
- transient rise in creatinine: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug

## Question 5 of 151

A 45-year-old female presents with a history of headache and generalised malaise for the last two months. She describes her headaches as being a tight band like sensation which is present almost throughout the day and causes significant difficulty in sleeping at night. She also mentions occasional episodes of vomiting along with low-grade fever and weight loss of about 7 kg over the same duration of time. She suffers from generalised anxiety disorder and takes 0.5mg alprazolam TDS. She returned from Dubai 9 months ago where she had been spending her holidays with her family.

On examination, she has a fever of 37.5°C and a pulse of 105bpm. She appears slightly disoriented with a tendency to speak out of context but is otherwise cooperative.

There is diplopia on right sided gaze and mild neck stiffness, but the remaining clinical examination is essentially unremarkable.

Lab reports reveal:

Hb 115 g/l

Platelets  $340 \times 10^9/l$

WBC  $9.0 \times 10^9/l$

Na<sup>+</sup> 137 mmol/l

K<sup>+</sup> 4.2 mmol/l

Urea 5.9 mmol/l

Creatinine 102 µmol/l

Glucose 7.0 mmol/l

ESR 87 mm/hr

MRI shows meningeal enhancement but no evidence of any parenchymal lesions.

CSF examination reveals:

Opening Pressure Normal

Appearance Turbid

Protein 3.2g/L (0.2-0.4 g/L)

Glucose 2.7 mmol/l

Lymphocytes 371/mm<sup>3</sup>

Neutrophils 42/mm<sup>3</sup>

ZN staining No acid fast bacilli detected

Which of the following is the most appropriate treatment option?

[IV acyclovir 25% IV ceftriaxone 13% Isoniazid, rifampicin, pyrazinamide and dexamethasone 48% IV benzylpenicillin 5% Artemether/lumefantrine 8%](#)

The 2-month history of headache, generalised malaise, low-grade fever and weight loss all go in favour of a diagnosis of tuberculous meningitis. This diagnosis is also supported by the examination findings of diplopia and neck stiffness.

The complete blood count does not favour a bacterial infection as one would expect a leucocytosis. The raised ESR is also supportive of TBM.

The CSF shows a predominant lymphocytosis with greatly raised protein and significantly low glucose which once again goes with tuberculosis.

TBM typically commences with symptoms of a vague headache, lassitude, anorexia and vomiting. Acute meningitis may occur but it is uncommon. The development of meningitic signs often takes weeks. Common signs include diplopia, papilloedema and hemiparesis and seizures are also often commonly seen. Treatment is generally commenced on a presumptive basis since multiple CSF cultures are often required and it may take weeks before culture reports are available. Staining with ZN staining is often negative and PCR for mycobacterium tuberculosis is helpful but is often negative too and repeat PCR is often needed.

Treatment is with isoniazid, rifampicin, pyrazinamide and steroids. Ethambutol should be avoided due to eye complications. Details regarding antimicrobial therapy and duration of treatment are available at <http://emedicine.medscape.com/article/1166190-treatment#aw2aab6b6b2>

## Meningitis: CSF analysis

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in meningitis:

	Bacterial	Viral	Tuberculous
<b>Appearance</b>	Cloudy	Clear/cloudy	Slight cloudy, fibrin web
<b>Glucose</b>	Low (< 1/2 plasma)	60-80% of plasma glucose*	Low (< 1/2 plasma)
<b>Protein</b>	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
<b>White cells</b>	10 - 5,000 polymorphs/mm <sup>3</sup>	15 - 1,000 lymphocytes/mm <sup>3</sup>	10 - 1,000 lymphocytes/mm <sup>3</sup>

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)

\*mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

### Question 6 of 151

A 35-year-old gentleman presents to the emergency department with worsening shortness of breath on exertion. His symptoms have been progressing for two weeks, and he now finds it difficult to take a full breath. He has no chest pain and has not been coughing but he has been feeling increasingly fatigued. He has a past medical history of HIV. He has been struggling to take his tablets recently. He is unsure of the names of any tablets, but he knows that he is supposed to take one tablet each day at the same time and to take two tablets twice a day on Mondays, Wednesdays, and Fridays. He has no other medical problems.

On examination, auscultation shows normal breath sounds.

Observations:

Saturations 93%

Respiratory rate 22/min

Blood pressure 136/71mmHg

Heart rate 91/min

Temperature 37.6°C

On mobilisation, his saturations reduce to 88%.

Chest X-ray is clear.

What investigation is most likely to be diagnostic?

[CT pulmonary angiogram6%High resolution CT chest17%ECG3%Echocardiogram6%Broncho-alveolar lavage68%](#)

The correct answer is broncho-alveolar lavage which is most likely to be able to demonstrate PCP characteristic cysts with silver staining. There are several factors highly suggestive of PCP. This gentleman is poorly compliant with his HIV medication and the other medication regime he is describing is PCP prophylaxis, suggesting a low CD4 count. He also is tachypnoeic with low saturations on mobilising and a clear chest X-ray. All of these factors suggest PCP. In the case of a productive cough, sputum could be obtained without the need for a broncho-alveolar lavage. Imaging can be suggestive of PCP but is not as sensitive or diagnostic as broncho-alveolar lavage. ECG and echocardiogram have no role in PCP diagnosis.

Source:

Nelson, M., Dh Dockrell, and S. Edwards. 'British HIV Association and British Infection Association Guidelines for the Treatment of Opportunistic Infection in HIV-seropositive Individuals 2011.' HIV Medicine 12 (2011): 1-5.

### **HIV: *Pneumocystis jiroveci* pneumonia**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count  $< 200/\text{mm}^3$  should receive PCP prophylaxis

#### Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

### Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

### Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if  $pO_2 < 9.3\text{kPa}$  then steroids reduce risk of respiratory failure by 50% and death by a third)



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

#### Question 7 of 151

A 38 year-old woman presented to the medical outpatient clinic with an 8 month history of deteriorating vision. She also complained of a pruritic rash intermittently affecting her forearms and neck. She had recently migrated to the UK from Guinea, where she had lived since birth. She had suffered from malaria as a child but had been fit and well since. She did not smoke and drank 6-10 units of alcohol per week.

On examination, her temperature was 36.7°C, pulse was 68 beats per minute and blood pressure was 124/80 mmHg. Her chest was clear on auscultation and heart sounds were normal. Fundoscopy was not possible due to clouding of both corneas. There was evidence of a mottled rash over the forearms and neck with a leopard print appearance.

#### Investigations:

Haemoglobin	141 g/L (130-180)
White cell count	$6.7 \times 10^9/L$ (4.0-11.0)

Neutrophil count 3.0 x <sup>9</sup>/L (2.0-7.5)  
 Lymphocyte count 1.7 x <sup>9</sup>/L (1.3-3.5)  
 Eosinophil count 0.6 X <sup>9</sup>/L (0.1-0.4)  
 Platelets 260 x <sup>9</sup>/L (150-400)

Sodium 138 mmol/L (135-145)  
 Potassium 4.3 mmol/L (3.5-5.0)  
 Urea 7.2 mmol/L (2.5-7.5)  
 Creatinine 61 mol/L (25-95)  
 Fasting plasma glucose 5.0 mmol/L (3.0-6.0)

Giemsa-stained blood film No abnormality detected

Given the likely diagnosis, what is the most appropriate treatment?

[Diethylcarbamazine](#)  
[\(DEC\)20% Ivermectin40% Benzinidazole11% Albendazole13% Praziquantel16%](#)

This patient has presented with features of onchocerciasis, a disease caused by the filarial nematode *Onchocerca volvulus*. The parasite is transmitted by blackflies of the genus *Simulium*, which deposit the parasites larva onto the skin when biting to extract blood. The adult worm lives in subcutaneous nodules and produces larvae, which become deposited in the skin and eyes. Disease manifests when the parasite dies in tissues and releases *Wolbachia* endosymbiotic bacteria into tissues, provoking a host immune response. This above patients disease has manifested as river blindness, where the worms die in the cornea and provoke chronic inflammation, eventually leading to clouding of the cornea. Inflammation in subcutaneous tissues leads to a pruritic rash and formation of a leopard-skin appearance over time. The worms can be visualised by microscopy of skin snip biopsy. The treatment of choice is ivermectin; DEC should not be used because rapid death of the worms can exacerbate damage to surround tissues and even cause complete blindness.

## Helminths

### Nematodes (roundworms)

Worm	Notes	Treatment
<i>Strongyloides stercoralis</i>	Larvae are present in soil and gain access to the body by penetrating the skin	Ivermectin and - bendazoles are used

Worm	Notes	Treatment
<i>Enterobius vermicularis</i> (pinworm)	<p>Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered</p> <p>Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms</p>	-bendazoles
<i>Ancylostoma duodenale, Necator americanus</i> (hookworms)	<p>Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs</p> <p>Larvae penetrate skin of feet; gastrointestinal infection → anaemia</p> <p>Thin-shelled ova</p> <p>Transmission by deer fly and mango fly</p>	-bendazoles
<i>Loa loa</i>	<p>Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae</p> <p>Typically develops after eating raw pork</p>	Diethylcarbamazine
<i>Trichinella spiralis</i>	<p>Features include fever, periorbital oedema and myositis (larvae encyst in muscle)</p> <p>Causes 'river blindness'. Spread by female blackflies</p>	-bendazoles
<i>Onchocerca volvulus</i>	<p>Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria</p> <p>Transmission by female mosquito</p>	Ivermectin r <b>IVER</b> blindness = <b>IVER</b> mectin
<i>Wuchereria bancrofti</i>	<p>Causes blockage of lymphatics → elephantiasis</p> <p>Transmitted through ingestion of infective eggs.</p>	Diethylcarbamazine
<i>Toxocara canis</i> (dog roundworm)	<p>Features include visceral larva migrans and retinal granulomas</p> <p>VISCious dogs → blindness</p> <p>Eggs are visible in faeces</p>	Diethylcarbamazine
<i>Ascaris lumbricoides</i> (giant roundworm)	May cause intestinal obstruction and occasional migrate to lung (Loeffler's syndrome)	-bendazoles



## Cestodes (tapeworms)

Worm	Notes	Treatment
<i>Echinococcus granulosus</i>	Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers.	-bendazoles
<i>Taenia solium</i>	Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal) Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
<i>Fasciola hepatica</i> (the liver fluke)	May cause biliary obstruction	Triclabendazole

## Trematodes (flukes)

Worm	Notes	Treatment
<i>Schistosoma haematobium</i>	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
<i>Paragonimus westermani</i>	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs Caused by undercooked fish	Praziquantel
<i>Clonorchis sinensis</i>	Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	Praziquantel

### Question 8 of 151

A 25-year-old man is seen in the walk-in travellers clinic. He returned from a holiday in Brazil 5 days ago and has a 1 day history of fever, headache and myalgia. He is usually fit and well. He tells you he took regular malaria prophylaxis while away.

On examination he has a heart rate of 110 beats per minute and a blood pressure of 102/72 mmHg. His temperature is 38.1 °C and he has dry mucous membranes. Examination of cardiovascular, respiratory and gastrointestinal systems is unremarkable but he has multiple

mosquito bites over his arms and legs.

His blood tests are as follows:

Hb	132 g/l	Na <sup>+</sup>	144 mmol/l	Bilirubin	8 µmol/l
Platelets	91 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.5 mmol/l	ALP	98 u/l
WBC	13 * 10 <sup>9</sup> /l	Urea	9.7 mmol/l	ALT	22 u/l
Neuts	11 * 10 <sup>9</sup> /l	Creatinine	111 µmol/l	γGT	14 u/l
Lymphs	0.6 * 10 <sup>9</sup> /l	CRP	78 mg/l	Albumin	40 g/l

He is admitted for broad spectrum antibiotics, fluids and analgesia but his fever continues. His malaria films are negative but he has a positive PCR for dengue virus. Antibiotics are stopped but fluids are continued. His fever and headache settle though he does developed some mild ankle oedema.

Which of the following is true regarding his discharge?

[Dengue shock is unlikely to occur after 24 hours post-fever9%](#)[Dengue shock is unlikely to occur once platelets improving29%](#)[Dengue shock is unlikely to occur once renal function improving13%](#)[Platelets above 20 \\* 10<sup>9</sup>/l are considered safe for discharge8%](#)[Stable haematocrit is essential for discharge40%](#)

This gentleman is admitted in the febrile phase of his dengue infection. The plasma leak phase may occur anytime within the first 48 hours after the fever has broken and manifests with leakage into pleural and peritoneal spaces. It may be accompanied by shock and in some cases haemorrhage. Platelets and renal function may be falsely reassuring as they tend to improve after the febrile phase but rising haematocrit is a sensitive sign of plasma leak. It is therefore essential to monitor patients for a full 48 hours after the febrile phase and ensure haematocrit is stable prior to discharge. Platelets should be at least 50 \* 10<sup>9</sup>/l and rising prior to discharge.

Reference: WHO guidelines for clinical management of Dengue infection

## Dengue fever

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

### Basics

- transmitted by the Aedes aegyti mosquito

- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

## Features

- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

## Question 9 of 151

A 29-year-old man presents to his first HIV clinic appointment. He has routine three month HIV tests. He received contact tracing notification last week and was tested and found to be HIV positive. He has just started antiretroviral treatment.

At clinic he mentions that he is due to go to South Africa. He hasn't yet had his travel vaccinations and is worried about what affect the new diagnosis of HIV will have on his travel plans. He is aware that currently immunosuppressed and at risk of infections and is committed to taking his tablets.

## Investigations:

Haemoglobin 113 g/L (130-180)  
 White cell count 6.5 10<sup>9</sup>/L (4.0-11.0)  
 Neutrophil count 5.4 10<sup>9</sup>/L (1.5-7.0)  
 Platelet count 170 10<sup>9</sup>/L (150-400)  
 CD4 count 180 cells/mm<sup>3</sup> (600-1500)

Which of the following vaccinations is safe to be given?

[Yellow fever 14% BCG 9% Oral polio 12% Meningococcal C 54% Varicella 11%](#)

Given this gentleman recent diagnosis with HIV he is immunocompromised which is reflected

by his low CD4 count. He should not be given live vaccines as he is at risk of disseminated infection.

Yellow Fever, BCG, Oral Polio and Varicella are all live vaccines. Meningococcal C is a conjugate vaccine and can be given cautiously to an immunocompromised patient.

## **HIV: immunisation**

The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

<b>Vaccines that can be used in all HIV-infected adults</b>	<b>Vaccines that can be used if CD4 &gt; 200</b>	<b>Contraindicated in HIV-infected adults</b>
Hepatitis A		
Hepatitis B		
<i>Haemophilus influenzae</i> B (Hib)		
Influenza-parenteral		
Japanese encephalitis	Measles, Mumps, Rubella (MMR)	Cholera CVD103-HgR
Meningococcus-MenC	Varicella	Influenza-intranasal
Meningococcus-ACWY I	Yellow Fever	Poliomyelitis-oral (OPV)
Pneumococcus-PPV23		Tuberculosis (BCG)
Poliomyelitis-parenteral (IPV)		
Rabies		
Tetanus-Diphtheria (Td)		

### **Question 10 of 151**

A 75-year-old male with a long history of intravenous drug use is admitted with fevers, rigors and back pain. Three sets of blood cultures taken at admission grow positive for gram positive cocci in clusters. He is suspected of having *Staphylococcus aureus* bacteraemia and is commenced on intravenous vancomycin.

Half an hour after the infusion is commenced, he is noted by the nurse to be flushed. On examination, he is noted to have erythema over his neck, face and trunk but denies any significant distress or discomfort.

His observations are as follow: blood pressure 125/70 mmHg, heart rate 85/min, temperature of

36.8°C, respiratory rate of 18/min and oxygen saturation of 98% on room air.

Which of the following is the most appropriate management?

[Stopping the vancomycin infusion, administering 200mg of IV hydrocortisone and informing the patient that he is allergic to the medication](#)10%[Stopping the vancomycin infusion and administering a single dose of 0.5mcg intramuscular adrenaline](#)5%[Stopping the vancomycin infusion until symptoms resolve and then re-starting a slower rate](#)64%[Stopping the vancomycin infusion and prescribing topical 1% hydrocortisone cream to affected areas](#)5%[Continuing the vancomycin infusion and administering 1000 ml of 0.9% saline solution over 1 hour](#)15%

Red man syndrome is associated with rapid intravenous infusion vancomycin. It is a common adverse reaction of intravenous vancomycin use and is a distinct entity from anaphylaxis due to vancomycin use. Typical symptoms include redness, pruritus and a burning sensation, predominantly in the upper body (face, neck and upper chest). Severe cases can be associated with hypotension and chest pain.

The pathophysiology of red man syndrome is attributed to vancomycin-related activation of mast cells with release of histamine.

The management of red man syndrome involves cessation of the infusion, and when symptoms have resolved, recommencement at a slower rate. In patients who are more symptomatic antihistamines can be administered, and may require intravenous fluids if the syndrome is associated with hypotension.

References:

- Sivagnanam S, Deleu D, Red man syndrome. Crit Care. 2003 Apr;7(2):119-20
- Bruneira FR, Ferreira FM, Saviolli LR, Bacci MR, Feder D, et al. The use of vancomycin with its therapeutic and adverse effects: a review Eur Rev Med Pharmacol Sci. 2015 Feb;19(4):694-700.

## **Vancomycin**

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).

Mechanism of action

- inhibits cell wall formation by binding to D-Ala-D-Ala moieties, preventing polymerization of peptidoglycans

#### Mechanism of resistance

- alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits (normally D-alanyl-D-alanine) to which the antibiotic binds

#### Adverse effects

- nephrotoxicity
- ototoxicity
- thrombophlebitis
- red man syndrome; occurs on rapid infusion of vancomycin

#### Question 1 of 141

A 35-year-old man presents to the genitourinary medicine clinic with a 1-week history of an ulcer on his penis. It is painless and he feels it might be increasing in size, though there are no other ulcers. He has never had any ulcers before.

He is HIV positive and remains sexually active with one regular male partner. They do not usually use condoms as he strictly adheres to his antiretroviral medication schedule and has an undetectable viral load.

He had gonorrhoea aged 18 which was treated with antibiotics at the time and he has no history of any other sexually transmitted infections.

He has no other past medical history and no drug allergies. He takes no medications other than his antiretrovirals.

On examination, he has a single shallow ulcer 1 x 2 cm on the dorsal surface of the penis with a small rim of surrounding erythema. He has no other rashes or lymphadenopathy. The systemic examination is otherwise unremarkable with no focal neurology.

Swabs from the ulcer are negative for herpes simplex virus 1 and 2.  
Penile swabs are negative for chlamydia and gonorrhoea.

Syphilis serology result:  
Enzyme immunoassay (EIA) +

Treponema Pallidum particle agglutination assay (TPPA) +  
Rapid plasma reagin (RPR) -

What is the best immediate management option?

[Intramuscular penicillin G and check repeat syphilis serology21%](#)  
[Intramuscular penicillin G and check syphilis PCR48%](#)  
[Check syphilis PCR12%](#)  
[Oral doxycycline and check repeat syphilis serology8%](#)  
[Oral doxycycline and check syphilis PCR11%](#)

This gentleman has a painless single penile ulcer which given negative testing for HSV, should be investigated for syphilis.

His syphilis serology shows a positive screening EIA and follow up TPPA (both treponemal-specific). However, his RPR titre is undetectable. This could indicate either past infection only or early acute infection without seroconversion on the RPR.

This gentleman is having unprotected intercourse and is HIV positive, so high risk for syphilis even if he gives a history of a single long-term partner. He also gives no history of past infection and so he should be treated for syphilis with antibiotics. Given he has no allergies, the first choice should be penicillin G.

However, for clarification regarding diagnosis, he requires further testing, the gold standard being syphilis PCR.

#### References:

Public Health England. (2015). Syphilis Serology. UK Standards for Microbiology Investigations. V 44 Issue 2. <https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories>

Centres for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines - Syphilis. 2015. Available online at: <http://www.cdc.gov/std/tg2015/syphilis.htm> (accessed 12 July 2015)

## Syphilis

Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. Infection is characterised by primary, secondary and tertiary stages. The incubation period is between 9-90 days

#### Primary features

- chancre - painless ulcer at the site of sexual contact

- local non-tender lymphadenopathy
- often not seen in women (the lesion may be on the cervix)

Secondary features - occurs 6-10 weeks after primary infection

- systemic symptoms: fevers, lymphadenopathy
- rash on trunk, palms and soles
- buccal 'snail track' ulcers (30%)
- condylomata lata



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Classical palm lesions of secondary syphilis





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More generalised rash of secondary syphilis

Tertiary features

- gummas (granulomatous lesions of the skin and bones)
- ascending aortic aneurysms
- general paralysis of the insane
- tabes dorsalis
- Argyll-Robertson pupil

Features of congenital syphilis

- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- saddle nose
- deafness

Question 2 of 141

A 25-year-old lady is admitted via the Emergency Department with shortness of breath, dry cough and wheeze. She has a past history of asthma and hayfever.

Her cough developed whilst on holiday in Cornwall a week ago. Since returning, she has visited her GP and been given a course of amoxicillin. She subsequently developed diarrhoea and headaches. None of her family has been unwell.

On examination she has saturations of 94% on air and a respiratory rate of 24/min. Her heart rate is 105/min and her blood pressure is 118/72 mmHg. Her temperature is 37.8 °C. She is able to complete sentences and her peak flow is 53% of her predicted. On auscultation she has right basal crepitations and widespread wheeze. Her abdomen is soft and non-tender with normal bowel sounds. She has multiple soft, mildly enlarged cervical lymph nodes but no palpable nodes elsewhere.

Her chest x-ray shows a right basal consolidation.

Her blood tests are as follows:

Hb	120 g/l	Na <sup>+</sup>	138 mmol/l	Bilirubin	4 µmol/l
Platelets	450 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.5 mmol/l	ALP	72 u/l
WBC	16 * 10 <sup>9</sup> /l	Urea	8 mmol/l	ALT	13 u/l
Neuts	14 * 10 <sup>9</sup> /l	Creatinine	82 µmol/l	CRP	35 mg/l

She is treated with salbutamol and ipratropium nebulisers, steroids and IV antibiotics.

Which test is most likely to reveal the causative organism?

[Blood cultures7%](#)[Legionella urinary antigen33%](#)[Mycoplasma serology37%](#)[Respiratory virus swab11%](#)[Sputum culture11%](#)

Although numerous bacteria and viruses can trigger asthma exacerbations, *Mycoplasma pneumoniae* is the most likely here. It is well documented to cause asthma exacerbations in the literature and this lady is experiencing headaches, lymphadenopathy and diarrhoea, which are all recognised extra-pulmonary manifestations of this infection.

Blood cultures may yield an organism in cases of typical bacterial infection but this lady is not profoundly septic and has only a low grade temperature. *Legionella* infection is more common in travellers returning from abroad and one would expect more severe signs of infection, with possible hyponatraemia, liver dysfunction and more severe gastrointestinal disturbance. Respiratory viruses are also known to cause asthma exacerbations but would not cause a lobar pneumonia on x-ray. Sputum culture in a patient with a dry cough is likely to grow only normal throat flora.

## References:

Blasi. Atypical pathogens and respiratory tract infections. Eur Resp J 2004; 24:171-81.

## ***Mycoplasma pneumoniae***

*Mycoplasma pneumoniae* is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

### Features

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

### Complications

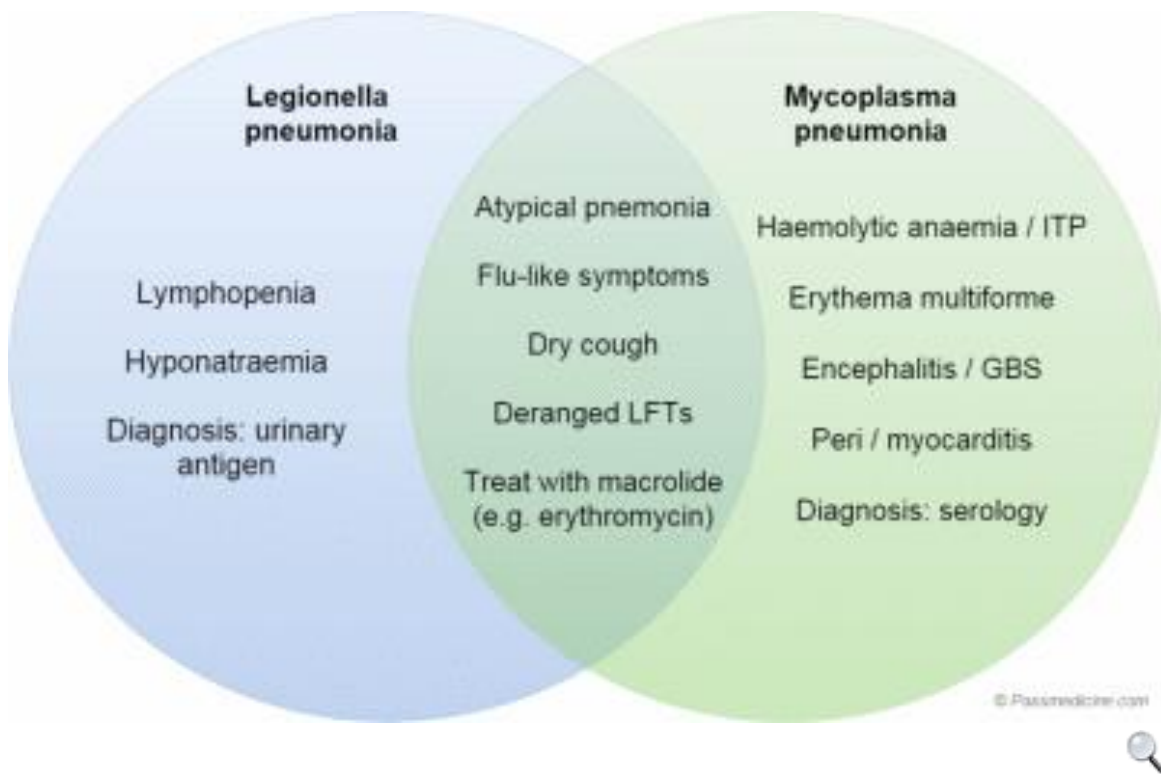
- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

### Investigations

- diagnosis is generally by *Mycoplasma* serology
- positive cold agglutination test

### Management

- erythromycin/clarithromycin
- tetracyclines such as doxycycline are an alternative



Comparison of Legionella and Mycoplasma pneumonia

Question 3 of 141

A 60 year old male who is a malnourished alcoholic presents with a chronic cough for the past 6 weeks associated with a low grade fever. The cough is productive of purulent sputum.

Six months previously he had been diagnosed with early stage non-Hodgkin's lymphoma, which had responded well to chemotherapy (doxorubicin, bleomycin, vinblastine, and prednisolone).

On examination his temperature is 37.8°C, blood pressure 140/80 mmHg, and his pulse is 96/minute and regular. Auscultation of the chest reveals absence of breath sounds over the left middle lung field. Chest x-ray confirms left upper lobar consolidation.

The following investigations were ordered:

Hb	12 g/dl
Platelets	$180 \times 10^9/l$
WBC	$7 \times 10^9/l$
MCV	85 fl

Na+ 140 mmol/l  
K+ 5 mmol/l  
Creatinine 90 µmol/l  
Urea 5 mmol/l  
CRP 50 mg/l

Sputum stains partially acid fast bacilli with branching rods

What is the most suitable initial management of this patient?

[Metronidazole + ampicillin8% Clarithromycin8% Ceftriaxone + clarithromycin11% Trimethoprim/sulfamethoxazole + amikacin + ceftriaxone35% Isoniazid + rifampin + pyrazinamide + ethambutol38%](#)

Nocardiosis typically occurs in immunocompromised patients with pulmonary involvement and in most cases with CNS or skin dissemination.

The clue here is the acid-fast stain which shows partially acid fast branching rods organism in contrast to mycobacterium which does fully stain.

Treatment of immunocompromised patients consists of multiple regimens. But mainly all of them involve Trimethoprim/sulfamethoxazole.

Nocardia species are ubiquitous soil organisms that often infect patients who are immunosuppressed, have pulmonary disease, or have a history of surgery or trauma. It is a Gram positive, acid fast bacilli.

### ***Actinomyces and Nocardia***

Both *Actinomyces* and *Nocardia* are Gram-positive rods that form fungus-like branched networks of hyphae-like filaments.

### ***Actinomyces israelii***

#### Basics

- chronic, progressive granulomatous disease caused by filamentous Gram-positive anaerobic bacteria from the *Actinomycetaceae* family.
- typically causes oral/facial abscesses with sulphur granules in sinus tracts
- may also cause an abdominal mass e.g. in the right iliac fossa

*Actinomyces* are commensal bacteria that become pathogenic when a mucosal barrier is breached.

The disease most commonly occurs in the head and neck, although it may also occur in the abdominal cavity and in the thorax.

The mass will often enlarge across tissue planes with the formation of multiple sinus tracts.

Abdominopelvic actinomycosis occurs most frequently in individuals that have had appendicitis (65%).

### Pathology

- On histological examination Gram-positive organisms and evidence of sulphur granules.
- Sulphur granules are colonies of organisms that appear as round or oval basophilic masses.
- They are also seen in other conditions such as nocardiosis

### Treatment

- Long-term antibiotic therapy usually with penicillin
- Surgical resection is indicated for extensive necrotic tissue, non-healing sinus tracts, abscesses or where biopsy is needed to exclude malignancy.

### References

Wong V, Turmezei T and Weston V. Actinomycosis. *BMJ* 2011;343d6099.

### *Nocardia*

#### Basics

- typically causes pneumonia in immunocompromised patients
- may also cause brain abscesses

A 30-year-old woman with rheumatoid arthritis has been diagnosed in the community with a prolonged urinary tract infection. For her rheumatoid arthritis she has been stable on azathioprine for nearly a year and besides paracetamol she takes no other regular medications.

The GP has requested a follow-up blood test which is shown below.

Baseline bloods were taken 2 months ago:

Hb 120 g/l  
Platelets  $310 \times 10^9/l$   
WBC  $4.5 \times 10^9/l$

Yesterday the bloods showed the following:

Hb 101 g/l  
Platelets  $296 \times 10^9/l$   
WBC  $1.9 \times 10^9/l$

Which of the following drugs is most likely responsible?

[Trimethoprim 62% Nitrofurantoin 21% Cephalexin 6% Amoxicillin 5% Co-amoxiclav 6%](#)

It is likely she has received a protracted course of antibiotics, possibly more than one different antibiotic even.

An important side effect of azathioprine is cytopenia. Azathioprine is metabolised to 6-mercaptopurine (6-MP) and then inactivated either by oxidation or methylation. Oxidation is catalysed by xanthine oxidase and methylation is catalysed by the enzyme TPMT. Factors that can lead to elevated levels of azathioprine are:

- Drugs that inhibit xanthine oxidase e.g. allopurinol
- Drugs that can also cause myelosuppression e.g. sulphonamides, trimethoprim
- Reduced activity of TPMT

## **Trimethoprim**

Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.

## Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase

## Adverse effects

- myelosuppression
- transient rise in creatinine: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug

## Question 5 of 141

A 27-year-old female with known HIV patient presents on the medical take with rigours, worsening cough and shortness of breath. She was diagnosed with pulmonary tuberculosis following a recent inpatient stay and discharged 1 month ago.

Lab results from her previous admission show a CD4 count of 120 and a viral load of 100,000 copies/mL. She was initially started on TB therapy and commenced HAART shortly before discharge.

On examination she has a temperature of 38.5°C, a heart rate of 92 beats per minute, a blood pressure of 118/76 mmHg, and a respiratory rate of 22/min. Auscultation of the chest reveals coarse crackles in the right mid and upper zone, there is also a dullness to percussion and quiet breath sounds at the right base. There is no lymphadenopathy and the remainder of the clinical examination is normal. A repeat chest x-ray today shows a worsening of right sided parenchymal consolidation and a new right sided pleural effusion.

What is the most appropriate management?

[Sputum drug sensitivity testing9%Drain the effusion and send fluid to microbiology for drug sensitivity testing35%Admit to hospital and organise directly observed therapy for her TB18%Add amphotericin 10%Add prednisolone 30mg PO OD28%](#)

This question is testing your ability to differentiate between drug resistance, poor compliance and the immune reconstitution inflammatory syndrome (IRIS).

Drug resistance in this situation is unlikely given that she has been an inpatient and safely discharged, this therefore assumes a clinical and microbiological improvement (for example transfer from smear negative to smear positive on sputum analysis). Drug sensitivity testing is usually done as standard in highly endemic areas.



Issues with compliance are common amongst TB patients due to the severity of side effects and the protracted nature of treatment. While this is possible issue here we are given extra information in the question that is pointing to another cause of her problems.

IRIS is a well recognised phenomenon that occurs when a recovering immune system recognises a foreign pathogen and creates an exaggerated immune response. This can manifest in 2 ways. unmasking IRIS occurs when there is silent, subclinical disease, HAART is started and the immune system recognises the disease and reacts causing fever and constitutional symptoms. Paradoxical IRIS occurs when there is recognised disease which is being treated (e.g. TB/Toxoplasmosis/cryptococcal meningitis), once HAART is started the immune system wakes from dormancy and goes into overdrive causing an apparent worsening of symptoms. With respect to TB this can cause pleural effusions and worsening radiological features. The treatment of IRIS involves continuing therapy and adding steroids to dampen the immune response. In extreme cases of IRIS there may be a argument for withholding HAART however this is exceptional and would only be done under specialist supervision.

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

### Protease inhibitors (PI)

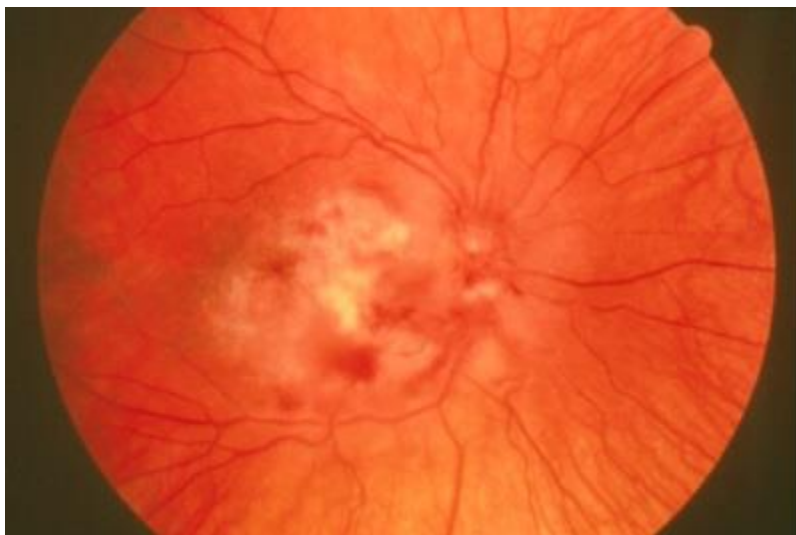
- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

### Question 7 of 141

A 42-year-old man who has recently emigrated to the UK is seen in the HIV clinic. He was diagnosed with HIV 5 years ago and has only sporadically taken anti-retroviral therapy during that period. He complains of blurred vision. Fundoscopy shows the following:



What is the most appropriate treatment?

[Intravenous ganciclovir 78%](#) [Oral pyrimethamine and sulfadiazine, plus folinic acid 8%](#) [Intravenous methylprednisolone 4%](#) [Oral mebendazole 4%](#) [Oral co-trimoxazole 5%](#)

The fundoscopic image shows changes consistent with cytomegalovirus retinitis.

### **HIV: Cytomegalovirus retinitis**

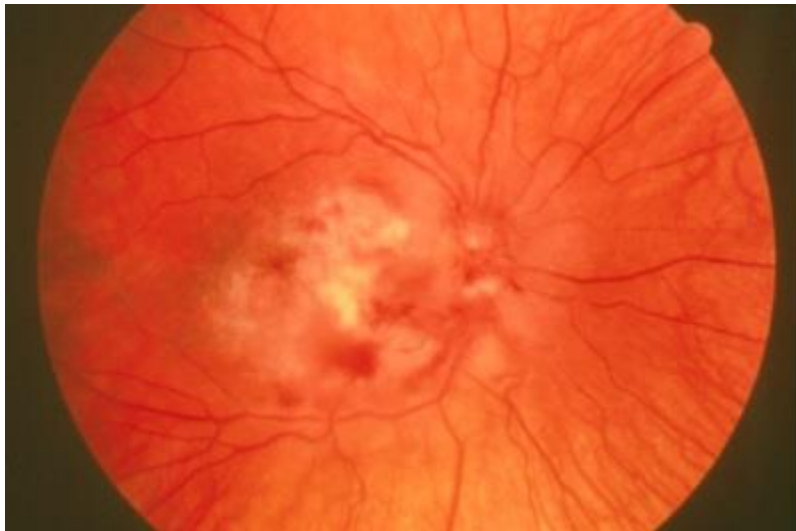
Cytomegalovirus (CMV) retinitis is common, affecting 30-40% of patients who have a CD4 count < 50. Diagnosis is clinical as there are no diagnostic tests

#### **Features**

- visual impairment - 'blurred vision' etc

#### **Fundoscopy**

- characteristic appearance showing retinal haemorrhages and necrosis
- often called 'pizza' retina



Fundus photograph showing CMV retinitis. Credit: National Eye Institute, National Institutes of Health

## Management

- IV ganciclovir
- treatment used to be life-long but new evidence suggests that it may be discontinued once CD4 > 150 after HAART
- alternative: IV foscarnet or cidofovir

### Question 8 of 141

A 54-year-old gentleman attends the Emergency Department, following a dog bite on his forearm 6 hours earlier. This occurred in the United Kingdom. The wound is clean with no active bleeding. There is no damage to underlying structures. He has no past medical history of note and does not take any regular medications. He has no known drugs allergies. He is unsure of his previous immunisation status. What is the most appropriate advice?

[Nothing additional required23% Rabies immunoglobulin17% Rabies vaccination18% Tetanus immunoglobulin13% Tetanus booster vaccination29%](#)

If a wound is considered clean then no further action is required if the patient has been fully vaccinated (i.e. 5 doses of tetanus vaccine at appropriate time intervals and booster vaccinations are up to date). Patients who are not fully immunised or are unsure of their vaccination history (as in the case) are advised to have a tetanus booster. For high-risk wounds e.g. If contamination with manure the same applies but they should also be given a tetanus immunoglobulin which will provide passive immunity. For all bite wounds or if any evidence of infection antibiotic prophylaxis should also be considered e.g. co-amoxiclav.

Rabies vaccination or immunoglobulin may be required if the bite occurred abroad depending on the risk level of that country.

All wounds should be thoroughly cleaned.

Source: BNF

## **Tetanus: vaccination**

The tetanus vaccine is a cell-free purified toxin that is normally given as part of a combined vaccine.

Tetanus vaccine is currently given in the UK as part of the routine immunisation schedule at:

- 2 months
- 3 months
- 4 months
- 3-5 years
- 13-18 years

This therefore provides 5 doses of tetanus-containing vaccine. Five doses is now considered to provide adequate long-term protection against tetanus.

Intramuscular human tetanus immunoglobulin should be given to patients with high-risk wounds (e.g. Compound fractures, delayed surgical intervention, significant degree of devitalised tissue) irrespective of whether 5 doses of tetanus vaccine have previously been given

If vaccination history is incomplete or unknown then a dose of tetanus vaccine should be given combined with intramuscular human tetanus immunoglobulin for high-risk wounds

#### Question 1 of 132

A 23-year-old woman presents to the emergency department. She was brought in by ambulance following left-sided weakness and difficulty in finding words. She also complains of a headache and nausea for the last three days. She has no past medical history and does not smoke nor does she drink alcohol. She recently emigrated from Tanzania to the UK.

On examination, she has marked weakness in upper and lower left limbs and is unable to walk without assistance. Her responses to questions are slow and limited.

Blood tests:

Hb	129 g/l
Platelets	$316 \times 10^9/l$
WBC	$8.9 \times 10^9/l$
Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	4.7 mmol/l
Urea	5.1 mmol/l
Creatinine	71 $\mu$ mol/l
HIV-1 serology	positive
HIV-2 serology	negative
HIV viral load	pending

CD4 count                      pending  
Toxoplasmosis serology pending  
Cryptococcal antigen      pending

A CT scan of her head demonstrates multiple ring-enhancing lesions and mass effect. Dexamethasone is started immediately. What is the most appropriate next step?

[Antiretroviral treatment7% Amphotericin5% Methotrexate5% MRI brain and whole spine4% Pyrimethamine and sulfadiazine80%](#)

The correct answer is pyrimethamine and sulfadiazine as the patient likely has cerebral toxoplasmosis as an AIDS-defining illness. Methotrexate is the treatment for a CNS lymphoma, alongside whole brain radiotherapy, but CNS lymphoma is unlikely since there are multiple lesions. Antiretroviral treatment will need to be started but should be done in specialist settings and not in the acute one. Further imaging would not be needed as there is sufficient evidence to start treatment at this point and would cause an unnecessary delay.

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



© Image used on license from [Radiopaedia](#)



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



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Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours





© Image used on license from [Radiopaedia](#)

Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



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Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
Thallium SPECT negative	Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 2 of 132

A 76-year-old female has been under the care of the medical team for the past week. She has been treated for a full sensitive *E. coli* bacteraemia with intravenous co-amoxiclav thought be sourced from the urinary system. On completing the course, the patient remains in for ongoing physiotherapy input. The next day, the patient has a temperature spike and cultures demonstrate regrowth of *E. coli*.

What is the most appropriate next step?

[Escalate antibiotics to meropenem30%](#) [Image the renal tract49%](#) [Commence treatment for hospital-acquired pneumonia7%](#) [Urology referral8%](#) [Urgent nephrostomy5%](#)

Discussion of this case with microbiology would likely result in the suggestion of imaging. In someone who has appropriate antimicrobial treatment, regrowth of the same organism would not be expected so soon. This may indicate there is a source of the bacteria that is not being adequately treated - a renal abscess in this case, which may be identified on ultrasound.

Escalation to meropenem should not be considered necessary if the organism has been fully sensitive to the narrower spectrum antibiotics.

*E. coli* would be an unlikely source of hospital-acquired pneumonia.

Urology referral would be the next step should a renal abscess be identified.

Imaging should first be carried out to determine whether a nephrostomy is required.

### ***Escherichia coli***

*Escherichia coli* is a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

*E. coli* infections lead to a variety of diseases in humans including:

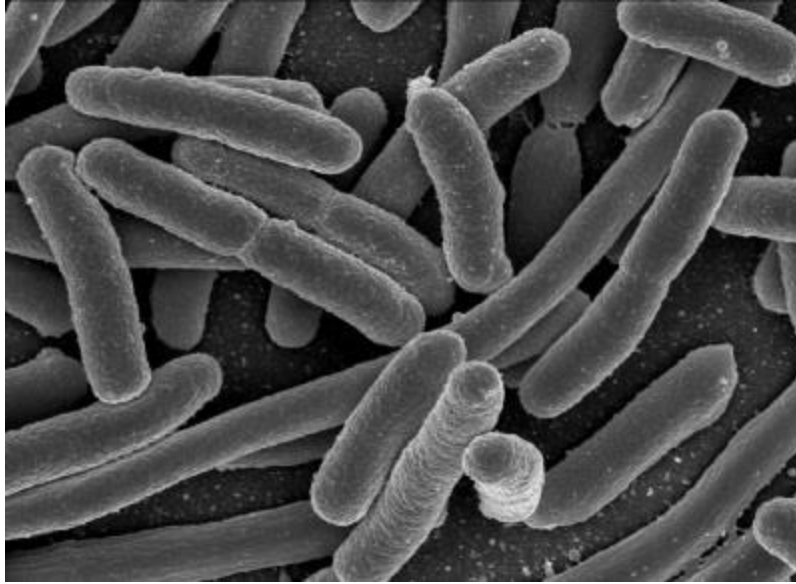
- diarrhoeal illnesses
- UTIs
- neonatal meningitis

### **Serotypes**

*E. coli* may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to <i>E. coli</i> is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

*E. coli* O157:H7 is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by haemolytic uraemic syndrome. It is often spread by contaminated ground beef.



Scanning electron micrograph of *Escherichia coli*, grown in culture and adhered to a cover slip.  
Credit: NIAID

### Question 3 of 132

A 19-year-old from Cameroon has moved to the UK to study nursing. She arrived three months ago. She has been having diarrhoea for a month and noticed a fleeting erythematous rash on her torso. Her GP orders a set of bloods, which reveal a dramatic eosinophilia. She has not lost weight and, if anything, seems concerned that she is becoming overweight since moving to the UK. She has been well previously with no allergies or medication. There is no significant family history but she tells you that her brother had an 'eye worm' last year.

A stool is sent for ova cysts and parasites and microscopy and culture. Multiple *Strongyloides stercoralis* larvae can be seen on charcoal culture. She is commenced on a seven-day course of Ivermectin.

Four days later she is brought into the Emergency Department, with a GCS of 6.

What is the diagnosis?

[Disseminated \*Strongyloides\* infection 20%](#) [Co-infection with \*Onchocerciasis\* 14%](#) [Co-infection with \*Loa\* 34%](#) [Ivermectin related hypoglycaemia 25%](#) [Insulin abuse 6%](#)

The give away in this history is the family history of 'eye worm'. This suggests that she lives in an area of high *Loa* *Loa* endemicity.

## Loiasis

Loiasis is a filarial infection caused by *Loa Loa*. It is transmitted by the *Chrysops* deerfly and tends to occur in rainforest regions of Western and Central Africa.

### Clinical features

- pruritus
- urticaria
- Calabar swellings: transient, non-erythematous, hot swelling of soft-tissue around joints
- 'eye worm' - the dramatic presentation of subconjunctival migration of the adult worm.

It has less pathological features than other the microfilarial infections *Onchocerciasis* and *Lymphatic Filariasis*. However high *loa loa* microfilaraemia is associated with encephalopathy following treatment with either Ivermectin or DEC. This occurs due to the death of vast numbers of blood microfilaria. Both of these drugs are contraindicated if *loa loa* microfilaraemia exceeds 2500 mf/ml.

This has significant public health implications as Ivermectin is currently the drug of choice for control of both *Onchocerciasis* and *Lymphatic Filariasis* in Africa.



Adult *Loa loa* parasite. *Loa loa* is the filarial nematode (roundworm) species that causes *loa loa* filariasis. It is commonly known as the 'eye worm.' Its geographic distribution includes Africa and India. Credit: NIAID

### Question 5 of 132

A 26-year-old pregnant woman is seen on the acute medical unit. She is 24 weeks pregnant with her first child and has been admitted by her GP after feeling generally unwell with 'flu like symptoms and developing jaundiced sclera. Her stay in Bangladesh lasted 2 weeks during which time she visited family. Prior to travelling she was vaccinated against hepatitis A.

On examination her sclera are visibly jaundiced. Blood pressure is 108/60 mmHg, temperature 38.1°C and pulse 96/min. She is slightly tender in the right upper quadrant of the abdomen. Bloods show the following:

Bilirubin 72 µmol/l

ALP 252 u/l

ALT 342 u/l

γGT 286 u/l

Albumin 38 g/l

CRP 154 mg/l

What is the most likely diagnosis?

[Dengue fever 10%](#) [Hepatitis E 64%](#) [Hepatitis A 7%](#) [Intrahepatic cholestasis of pregnancy 11%](#) [Acute fatty liver 8%](#)

Hepatitis E is more likely to cause severe disease in pregnant women. Hepatitis A is unlikely given her previous immunisation against this. There are no other features to support the remaining three distractors.

## Hepatitis E

### Overview

- RNA hepevirus
- spread by the faecal-oral route
- incubation period: 3-8 weeks
- common in Central and South-East Asia, North and West Africa, and in Mexico
- causes a similar disease to hepatitis A, but carries a significant mortality (about 20%) during pregnancy

- does not cause chronic disease or an increased risk of hepatocellular cancer
- a vaccine is currently in development\*, but is not yet in widespread use

\*New England Journal of Medicine 356:895, 2007

#### Question 8 of 132

A 14 week pregnant woman attends her GP describing significant contact 2 days ago with a friend's daughter, who has been diagnosed with chickenpox. When questioned, she informs the GP that she has never had chickenpox before. Her GP arranges serological testing for varicella zoster virus (VZV), which confirms that she is non-immune. What would be the most appropriate management?

[Aciclovir & varicella-zoster immunoglobulin \(VZIG\) as soon as possible 21% VZIG as soon as possible 61% No treatment needed, as more than 24 hours since contact occurred 5% VZIG if she develops chickenpox rash 5% Varicella vaccine 9%](#)

When contact occurs with chickenpox or shingles in a pregnancy, it is paramount to take a detailed history in order to confirm the significance of the exposure and susceptibility of the patient.

An individual will be potentially susceptible if they are uncertain or have no previous history of chickenpox. These patients should have their blood tested to determine VZV immunity or non-immunity. Significant exposure to chickenpox includes having face-to-face contact, being in the same room for 15 minutes or more, or in a large open ward. It is also important to enquire about contact before the chickenpox rash develops (as infectivity begins 2 days before the onset of the rash until lesions crust).

If exposure is deemed to be significant and the pregnant woman is non-immune, then VZIG should be given within 10 days of the exposure. The purpose of VZIG is to help prevent or attenuate chickenpox in non-immune individuals. VZIG has no therapeutic benefit once the chickenpox rash has started. Aciclovir can be given within 24 hours of the onset of the rash.

If a pregnant woman has a clear history of previous chickenpox, then no further action is required.

Varicella vaccination can be offered postpartum for women who are found to be non-immune to VZV. It is contraindicated in pregnancy, as it is a live vaccine.

RCOG Greentop guidelines, Chickenpox in pregnancy.



## **Chickenpox exposure in pregnancy**

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion. In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

### **Risks to the mother**

- 5 times greater risk of pneumonitis

### **Fetal varicella syndrome (FVS)**

- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

### **Other risks to the fetus**

- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester
- severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

### **Management of chickenpox exposure**

- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently checked for varicella antibodies
- if the pregnant woman is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure
- consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

Question 2 of 122

A 33-year-old man who is HIV positive is admitted to the Emergency Department with confusion and drowsiness. He has been complaining of headaches for a number of days. On examination heart rate is 90/min, blood pressure 104/78 mmHg and temperature is 37.2°C. He is confused giving a Glasgow Coma Scale (GCS) score of 14. There is no photophobia or neck stiffness.

His infectious diseases consultant reports that he is prescribed highly active antiretroviral treatment (HAART) but his compliance is poor and he often misses clinic appointments.

A CT scan is requested:



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What is the most likely diagnosis?

[Cerebral toxoplasmosis52%](#) [Tuberculosis5%](#) [CMV encephalitis9%](#) [Progressive multifocal leukoencephalopathy24%](#) [Cryptococcal infection11%](#)

HIV - multiple ring enhancing lesions = toxoplasmosis

The CT scan shows multiple ring enhancing lesions consistent with cerebral toxoplasmosis. He is at risk of this due to his poor compliance with medication.

Cerebral toxoplasmosis is the most common neurological infection seen in HIV, occurring in up to 10% of patients.

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



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Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

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Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



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**Generalised neurological disease**

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- HSV encephalitis but is relatively rare in the context of HIV
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## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 3 of 122

A 66 year old lady, originally from Pakistan, has lived in the UK for 10 years. She has type 2 diabetes mellitus which is controlled with metformin only.

For the last few years she has had multiple lumps over her whole body but this hasn't bothered her as it has been there for several years and not got too much worse. She has been seeing the diabetic foot care team due to several traumatic slow healing ulcers on her feet.

Over the past few weeks she has been feeling increasingly unwell. She has had a fever, pain in

her knees and elbows, sore painful eyes. She also complains of painful swelling in her ring and little fingers on her right hand.

On examination her temperature is 37.8C. Her pulse is 91 beats/minute and her RR is 18 breaths/minute. Her oxygen saturations are 97% on room air.

She has a multiple nodular lesions over her whole body in a symmetrical distribution. Sizes of these nodule range from 2cm - 4cm. These lesions are not painful, in fact with the larger ones she is unable to feel you touching them. On her shins there are several hot painful nodules which are uncomfortable to touch. She has a saddle deformity of her nose. There are several scars on her hands, and an ulcer on the lateral dorsum of her foot. Cardiorespiratory and abdominal examination is essentially normal. Both knees and elbow are slightly erythematous and swollen. She has weakness abducting her little and index finger on her left hand and has no sensation in her left little finger. There is a non-painful 1x4 cm lump two centimetres distal to her left medial epicondyle.

Urinalysis reveals ++ of protein and + of blood.

Blood sugar: 8.8 mmol/L

On the clinical information alone what investigation is most likely to secure the diagnosis?

[Serum cANCA antibody20%Serum dsDNA antibody9%Renal biopsy 11%Skin biopsy 54%Serum ANA antibody6%](#)

With skin lesions and peripheral nerve involvement leprosy should certainly be on a differential diagnosis. Other give away features here are the anaesthetic skin lesions and nerve thickening. The erythema nodosum like lesions and the joint, renal and conjunctival involvement indicate a type 2 reaction which occur in patients with lepromatous leprosy (usually following treatment).

Skin biopsy in this case will reveal the diagnosis. This would save her the potentially disastrous consequences of immunosuppression.

## **Leprosy**

Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*.

Features



- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

The degree of cell mediated immunity determines the type of leprosy a patient will develop.

Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')

- extensive skin involvement
- symmetrical nerve involvement

High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')

- limited skin disease
- asymmetric nerve involvement

## Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine

## Question 4 of 122

A 63 year old man, originally from Ukraine is admitted to hospital with a right sided pleural effusion. On admission he is febrile at 37.8 C. He reports 6kg of weight loss, and night sweats over the previous 4 months.

His pleural effusion is exudative with a pH of 7.4.

A CT chest/abdo/pelvis reveals a right sided pleural effusion, multiple enlarged lymph nodes in his abdomen and mediastinum. A pleural biopsy reveals scanty Acid Fast Bacilli and he is commenced on treatment for tuberculosis with Rifampicin, Isoniazid, Ethambutol, Pyrazinamide. PCR confirms this to be Mycobacterial Tuberculosis complex with wild type rpoB, katG, inhA genes. His HIV serology is positive and his CD4 count is 47 cells/mm<sup>3</sup>

One week following admission he is commenced on anti-retroviral treatment with Emtricitabine, Lamivudine and Efavirenz with Co-trimoxazole.

Three weeks later he becomes more unwell. He has daily fevers up to 39°C.

On examination he is febrile 38.1 with an associated tachycardia of 119 beats/min, his blood pressure is 112/67 mmHg and respiratory rate is 22 breaths/min. His oxygen saturations are 93%. He has reduced air entry at the right base, but no other abnormality on examinations.

His results are as following:

Hb	10.1 g/dl
MCV	82 fl
Platelets	$97 \times 10^9/l$
WBC	$7.8 \times 10^9/l$
Neutrophils	$6.3 \times 10^9/l$
Lymphocytes	$1.2 \times 10^9/l$
Eosinophils	$0.02 \times 10^9/l$
ESR	62 mm/hr

Bilirubin	9 $\mu\text{mol/l}$
ALP	312 u/l
ALT	153 u/l
$\gamma\text{GT}$	456 u/l
Albumin	22 g/l
CRP	67 mg/l
Lactate	1.1 mmol/l

Other results were as follows;

Urea and electrolytes: normal.  
Clotting screen: normal  
Blood cultures: negative (x3)  
Urinalysis: normal  
ECHO: normal  
CXR: right pleural effusion  
USS abdo: several abdominal nodes visible, nil else.  
Toxoplasmosis serology: negative  
CMV: IgG negative IgM: negative  
EBV: IgG positive IgM: negative  
Cryptococcal antigen: Negative  
Leishmania serology: negative

What is the most likely diagnosis?

[Pneumococcal pneumonia 5%](#)[Drug resistant tuberculosis 10%](#)[Infectious mononucleosis 5%](#)[Immune reconstitution inflammatory syndrome 72%](#)[Burkitts Lymphoma 8%](#)

This is a classic history of Immune Reconstitution Inflammatory syndrome (IRIS). IRIS is a paradoxical worsening of symptoms, due to increasing inflammatory activity with a recovering immune system. It is seen in the context of anti-retroviral therapy.

In this case we are reassured of a correct diagnosis to TB with the PCR result, and the initial PCR results suggest a fully susceptible organism (although this will need to be confirmed by culture and sensitivity testing.) You may not have a luxury of a confident diagnosis of TB, and patients with HIV may have many different opportunistic infections. Therefore IRIS is a diagnosis of exclusion. In this case an extensive screen has revealed no alternative cause for his symptoms.

The diagnosis of IRIS depends on all three of :

1. Antecedants:

- Diagnosis of TB fulfilling WHO clinical criteria
- Initial response to anti-retroviral treatment

2. Clinical (1 major criteria or 2 minor)

Major: New or worsening cold abscess lymph nodes, radiological features of TB, CNS TB or TB serositis

Minor: New or worsening constitutional symptoms, respiratory symptoms or abdominal pain.

3. Alternative explanations for clinical deterioration must be excluded.

## **Immune reconstitution inflammatory syndrome**

Immune reconstitution inflammatory syndrome is a condition generally associated with HIV/immunosuppression, in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.

Question 5 of 122

A 37 year old Caucasian male attends an outpatient clinic. He had recently spent three months in Jamaica on a beach-side yoga retreat. He only drank bottled water and ate well cooked vegetarian food. He ensured that any raw vegetables were peeled. He returned home three weeks ago.

During his final week in Jamaica he noticed an itchy spot develop on the side of his ankle. The rash has gradually spread from the original spot slowly 'like a snake up the side of his foot'. The lesion is currently 11cm long and is a raised itchy serpiginous linear lesion.

He is otherwise well.

What is the causative organism?

[Strongyloides stercoralis 28%](#)[Ancylostoma braziliense 29%](#)[Necator americanus 13%](#)[Ascaris lumbricoides 20%](#)[Schistosomiasis mansoni 10%](#)

### **Cutaneous larva migrans**

Cutaneous Larva Migrans is caused by the infection of the dog hook worm *Ancylostoma Braziliense*.

Man is an accidental dead end host and so the larva is unable to migrate to the lungs and intestine. The intensely itchy trail is a result of the subcutaneous migration of the frustrated larva.

Management is with Albendazole or Ivermectin.

Question 1 of 117

A 42-year-old man with genotype 4 hepatitis C and early hepatic fibrosis on liver biopsy comes to the clinic to discuss the preferred options for anti-viral therapy. His LFTs have been stable over the past few months and results are shown below;

Bilirubin 11  $\mu\text{mol/l}$

ALP 141 u/l

ALT 82 u/l

$\gamma\text{GT}$  89 u/l

Albumin 37 g/l

Which of the following is the most appropriate intervention?

[Simeprevir, interferon alpha and ribavirin30% Interferon alpha and lamivudine11% Interferon alpha and ribavirin35% Ribavirin and lamivudine15% Grazoprevir and lamivudine8%](#)

Simeprevir is a NS3/4A hepatitis C virus (HCV) protease inhibitor, a cornerstone of modern management for hepatitis C. It is recommended by NICE for genotypes 1 and 4 in combination with interferon alpha and ribavirin.

Lamivudine and interferon alpha in combination were a combination treatment used historically for hepatitis B. Interferon alpha and ribavirin. Dual therapy with interferon alpha and ribavirin was historically used for hepatitis C, but this has now been replaced by the targeted newer agents. Ribavirin and lamivudine are not used in combination for hepatitis C. Grazoprevir is an NS3/4a protease inhibitor used in hepatitis C treatment, it is not usually used in combination with lamivudine however.

<https://www.evidence.nhs.uk/formulary/bnf/current/5-infections/53-antiviral-drugs/533-viral-hepatitis/5332-chronic-hepatitis-c/simeprevir>

## Hepatitis C

Hepatitis C is likely to become a significant public health problem in the UK in the next decade. It is thought around 200,000 people are chronically infected with the virus. At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

### Pathophysiology

- hepatitis C is a RNA flavivirus
- incubation period: 6-9 weeks

### Transmission

- the risk of transmission during a needle stick injury is about 2%
- the vertical transmission rate from mother to child is about 6%. The risk is higher if there is coexistent HIV
- breast feeding is not contraindicated in mothers with hepatitis C
- the risk of transmitting the virus during sexual intercourse is probably less than 5%

After exposure to the hepatitis C virus only around 30% of patients will develop features such as:

- a transient rise in serum aminotransferases / jaundice
- fatigue
- arthralgia

### Investigations

- HCV RNA is the investigation of choice to diagnose acute infection
- whilst patients will eventually develop anti-HCV antibodies it should be remembered that patients who spontaneously clear the virus will continue to have anti-HCV antibodies

### Outcome

- around 15-45% of patients will clear the virus after an acute infection (depending on their age and underlying health) and hence the majority (55-85%) will develop chronic hepatitis C

## Chronic hepatitis C

Chronic hepatitis C may be defined as the persistence of HCV RNA in the blood for 6 months.

### Potential complications of chronic hepatitis C

- rheumatological problems: arthralgia, arthritis
- eye problems: Sjogren's syndrome
- cirrhosis (5-20% of those with chronic disease)
- hepatocellular cancer
- cryoglobulinaemia: typically type II (mixed monoclonal and polyclonal)
- porphyria cutanea tarda (PCT): it is increasingly recognised that PCT may develop in patients with hepatitis C, especially if there are other factors such as alcohol abuse
- membranoproliferative glomerulonephritis

## Management of chronic infection

- treatment depends on the viral genotype - this should be tested prior to treatment
- the management of hepatitis C has advanced rapidly in recent years resulting in clearance rates of around 95%. Interferon based treatments are no longer recommended
- the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy
- currently a combination of protease inhibitors (e.g. daclatasvir + sofosbuvir or sofosbuvir + simeprevir) with or without ribavirin are used

## Complications of treatment

- ribavirin - side-effects: haemolytic anaemia, cough. Women should not become pregnant within 6 months of stopping ribavirin as it is teratogenic
- interferon alpha - side-effects: flu-like symptoms, depression, fatigue, leukopenia, thrombocytopenia

## Question 2 of 117

A 42-year-old male from Bolivia presents with a 8 month history of progressive fatigue, dyspnoea and intermittent chest pains. He is a chronic smoker and during a recent severe episode of breathlessness had consulted his GP who prescribed amoxicillin and prednisolone to combine with his regular inhaler therapy. Shortly after this he experienced a febrile episode which had lasted 7 days before resolving. His breathlessness also worsened during this period.

On examination he has a temperature of 37.2 degrees, a heart rate of 98 beats per minute, a blood pressure of 110/70 mmHg and a respiratory rate of 24/min. His jugular venous pressure was raised, there was lower limb oedema to the mid shin and a pan systolic murmur heard best in inspiration in the left parasternal region. An ECG showed a prolonged PR interval.

What is the most likely underlying diagnosis?

[Ischaemic heart disease4%](#)[Chronic pulmonary emboli5%](#)[Chronic Chagas cardiomyopathy80%](#)[Sarcoidosis7%](#)[HIV4%](#)

Teasing out the infective aetiology in this question is the key to finding the answer. Chagas disease can present as an acute illness or as a chronic disease years after infection and is caused by the parasite *Trypanosoma cruzi*.

Acute disease is usually asymptomatic but may manifest as a febrile episode in association with a swelling over the site of inoculation (if in the skin this is called a chagoma if through the conjunctiva of the eye this is known as Romanas sign). In severe cases an acute myocarditis can evolve with a secondary pericardial effusion.

Chronic disease begins to develop weeks or months after the initial inoculation and in some cases does not present until years after the infection (as in this case). Chronic disease can effect the heart causing a biventricular cardiomyopathy with predominant right sided features as well as varying degrees of heart block and conductive abnormalities due to fibrous inflammation around amastigotes embedded in the heart muscle. Chest pain can also be common and does not imply an ischaemic component. Chronic disease can also effect the bowel causing dilation.

The first clue in the case is that the patient is from an area where disease is endemic. Secondly there is an absence of ischaemic related risk factors other than his smoking history and he is of a relatively young age. Perhaps the biggest clue of an infective cause is the febrile episode following steroids therapy. This likely represents a relapse of acute infection which is common with immunosuppression. At this point you may be able to see trypomastigotes in the blood but they soon disappear on resolution of the fever.

Chronic PE is also a possibility given the predominance of right sided signs but does not explain the first degree heart block or fever following steroid therapy.

## Trypanosomiasis

Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly. *Trypanosoma rhodesiense* tends to follow a more acute course. Clinical features include:

- Trypanosoma chancre - painless subcutaneous nodule at site of infection
- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis

## Management



- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract

- myocarditis may lead to dilated cardiomyopathy (with apical atrophy) and arrhythmias
- gastrointestinal features includes megaoesophagus and megacolon causing dysphagia and constipation

### Management

- treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure

### Question 3 of 117

A 72-year-old man presents to the tuberculosis clinic.

He has a 6-month history of lower back pain that has been gradually getting worse. He has tried taking analgesia, but this is now no longer helping the pain and he is becoming less able to mobilise.

He lives with his wife on their farm. He has been fully independent until his recent deterioration in mobility.

Past medical history includes hypertension, diet-controlled type 2 diabetes mellitus and benign prostatic hypertrophy.

He reports that he had tuberculosis when he was 24, but this was treated. He can't remember what he was treated with.

An MRI spine shows a lumbar 4/5 discitis and a biopsy of this tissue is arranged. Acid-fast bacilli are grown on culture of the biopsy.

What treatment regime should be started?

2 months of isoniazid, rifampicin, pyrazinamide and ethambutol with a further 4 months of isoniazid and rifampicin32%6 months of isoniazid, rifampicin, pyrazinamide and ethambutol with a further 6 months of isoniazid and rifampicin29%6 months of isoniazid, rifampicin, pyrazinamide and ethambutol7%2 months of isoniazid, rifampicin, pyrazinamide and ethambutol with a further 7 months of isoniazid and rifampicin19%3 months of isoniazid, rifampicin, pyrazinamide and ethambutol with a further 6 months of isoniazid and rifampicin14%

Treatment for bone and joint tuberculosis is recommended to continue for 2 months with the initial phase consisting of quadruple therapy and the remaining 4 months of dual therapy.

It is recommended not to extend treatment for residual complications such as collapsed discs or bending of the spine, although there is some debate about this.

<https://www.nice.org.uk/guidance/ng33/chapter/Recommendations#active-tb>

## **Tuberculosis: management**

Stop medication if LFT's > 5 times normal limit

Immune reconstitution disease

- occurs typically 3-6 weeks after starting treatment
- often presents with enlarging lymph nodes

### **Question 4 of 117**

An 80-year-old gentleman presented with a 4 month history of feeling generally unwell, being more breathless and tired than usual, feeling feverish and having a dry cough. He had already been treated by the General Practitioner with 2 courses of antibiotics in the community with only temporary improvement. His past medical history includes previous myocardial infarction, permanent pacemaker (PPM) with box-change 8 months ago, hypertension, diabetes, anaemia and chronic kidney disease (stage 2). He is a lifelong smoker.

On examination his heart sounds were normal with no murmurs, he had scattered crackles and his abdomen was soft and non-tender. There was mild leg oedema and a faint purpuric rash on his shins. His vital signs revealed heart rate = 80 beats per minute, blood pressure = 130/70 mmHg, T=37.8oC, SaO2 = 96% on air and respiratory rate = 20 breaths per minute. His chest X-

ray did not show and consolidation and his urine was clear.

The following blood tests have been obtained:

Hb	10.5 g/dl
MCV	95 fl
Platelets	$160 \times 10^9/l$
WBC	$13.4 \times 10^9/l$
Na <sup>+</sup>	132 mmol/l
K <sup>+</sup>	4.9 mmol/l
Urea	12 mmol/l
Creatinine	150 $\mu$ mol/l
CRP	100 mg/l

Blood cultures grow coagulase negative staphylococci and you notice that during his previous admission in the hospital he also had positive blood cultures for coagulase-negative staphylococci.

What is the best next investigation?

[Repeat blood cultures9%Computed tomography thorax / abdomen / pelvis9%Biopsy of the rash6%Vasculitic screen9%Urgent transoesophageal echocardiogram67%](#)

This question aims to raise awareness of the significance of blood cultures positive for coagulase-negative staphylococci.

Coagulase-negative staphylococci are often considered skin contaminant or apathogenic organisms. However, in the presence of prosthetic devices such as PPM, prosthetic heart valves, central venous lines and orthopaedic prostheses they are the commonest cause of infection causing device-related infection. This is because of their ability to establish biofilms on artificial layers. *Staphylococcus epidermidis* device-related infections: pathogenesis and clinical management, JPP 2008, 60:1551-1571

This patient presented with symptoms and signs suggestive of a chronic infection and had blood cultures positive for coagulase-negative staphylococci. The presence of the PPM and the purpuric rash indicate that the source of sepsis is possibly related to the medical device. The box-change also increases the risk of infection.

Repeating the blood cultures is a good idea but it does not help identify the source of sepsis. CT thorax / abdomen / pelvis is an investigation that can identify most sources of sepsis especially if there is a clinical suspicion of lung or intra-abdominal abscess. However, in this case, it will not be particularly useful to verify the source of sepsis. Vasculitis is less likely in that scenario and so biopsy of the rash or vasculitic screen should not be the next investigation.

Transoesophageal echocardiogram is the best investigation to rule out pacemaker-wire related infections. It requires a lot of expertise and it might not be readily available but even so it is the next best investigation in this scenario. Please see the following article for further information. Update on Cardiovascular Implantable Electronic Device Infections and Their Management: A Scientific Statement From the American Heart Association, Circulation. 2010; 121: 458-477

## **Staphylococci**

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease. Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase

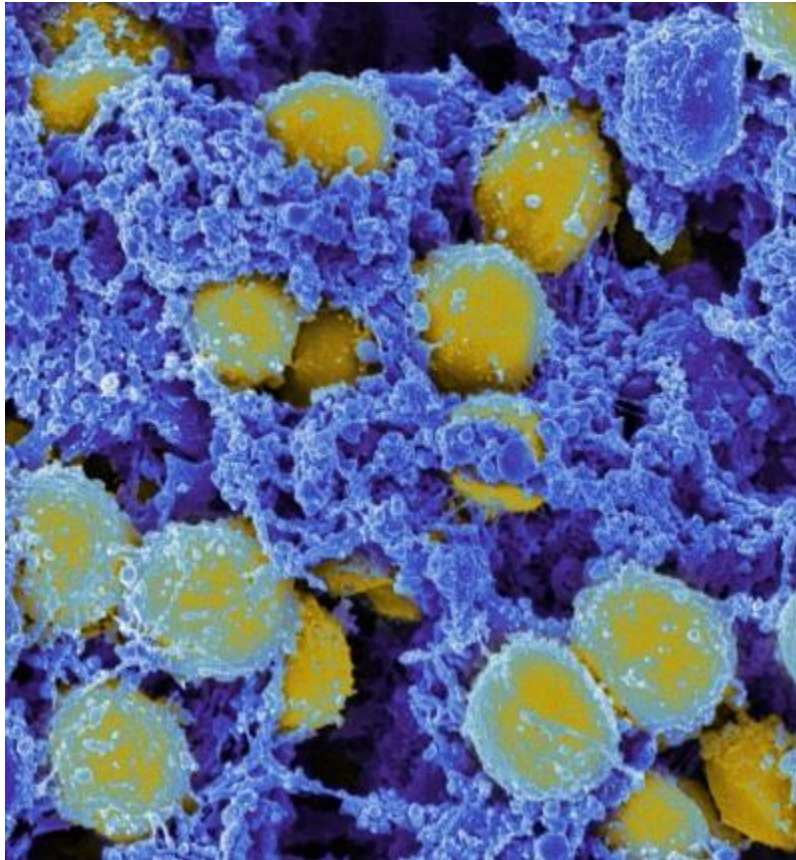
The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

### ***Staphylococcus aureus***

- Coagulase-positive
- Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome

### ***Staphylococcus epidermidis***

- Coagulase-negative
- Cause of central line infections and infective endocarditis



Scanning electromicrograph of Staphylococcus aureus bacteria. Credit: NIAID

#### Question 5 of 117

A 24-year-old Caucasian girl returned from a two week scuba diving holiday in Honduras four days ago. She had not taken malaria prophylaxis. She had been drinking alcohol moderately during her trip. She had unprotected sex during her holiday with her diving instructor.

Yesterday she had felt hot and cold with pain all over her body and a headache. Today the pain is worst behind her eyes. It is a constant pain and there is no photophobia or neck stiffness. She has an erythematous rash over her trunk and back with patches of white skin surrounded by erythema. There is no lymphadenopathy

She is observed in hospital for 48 hours and tests for HIV (including PCR and antibody), malaria and blood cultures were negative. Further tests remain unreported.

She recovers and is feeling much better. Prior to discharge, she asks if she is safe to go back to Honduras next year.

What should you advise?

She should not go back to any Dengue endemic area as there is a risk of Dengue haemorrhagic fever (with a 20% mortality) with a second exposure to Dengue virus26%She can go back to Honduras, although there is a small risk of Dengue haemorrhagic fever with a second exposure, the risk is small enough not to be overly worried. She should take precautions not to be bitten by mosquitos during the day53%She has had Dengue fever so will be immune to Dengue fever on subsequent exposure9%She has had flu and therefore she can go back to Honduras next year5%Staying in the UK from now on would be the most sensible given that she is at high risk of malaria, HIV and Dengue fever from her behavioral tendencies7%

There are four serovars of Dengue (1-4) and therefore infection with one serovar will not confer immunity to the other serovars. There is a theoretical risk that consequent infection with serovar 2 following infection with serovar 1 will increase your risk of progression to Dengue Haemorrhagic Fever. However, the risk is far smaller than other risks posed by travelling (e.g road traffic accident, acquiring HIV from unprotected sex etc.) Therefore universal travel advice (including avoidance of day biting mosquitos) is appropriate.

## **Dengue fever**

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

### **Basics**

- transmitted by the Aedes aegypti mosquito
- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

### **Features**

- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

#### Question 6 of 117

You are asked to review a patient on the ward who the nurse feels is looking very flushed. The nurse noticed the change in the patient whilst they were receiving their first dose of vancomycin. On examination the patient has no symptoms or signs of cardiorespiratory distress. Observations are as follows:

Temperature 37.2 °c

Respiratory rate 18 breaths/min

Saturations on air 97%

Heart rate 70 beats/min

Blood Pressure 136/72 mmHg

A blanching macular rash is evident on the patient's upper arms and upper thighs. No signs of urticaria or excoriations. The patient is penicillin allergic.

What is your next step?

[Measure mast cell tryptase levels7%](#)[Stop the infusion, give the patient piriton and hydrocortisone15%](#)[Stop the infusion and give the patient piriton, hydrocortisone, adrenaline6%](#)[Continue the infusion but slow it down and give the patient piriton61%](#)[Stop the infusion, do not give any further treatment but discuss an alternative antibiotic with microbiology12%](#)

The most likely explanation for the patient's condition is a drug reaction called red man syndrome secondary to vancomycin infusion. This is not an allergic reaction as demonstrated by the lack of cardiorespiratory distress, subcutaneous oedema, wheals or urticaria. The reaction is more of a rate dependent infusion reaction. Treatment involves slowing down the infusion of vancomycin and administration of anti-histamines.

Further information about red man syndrome can be found at the following sources:

BNF: <https://www.evidence.nhs.uk/formulary/bnf/current/5-infections/51-antibacterial-drugs/517-some-other-antibacterials/glycopeptides/vancomycin><http://www.uptodate.com/contents/vancomycin-hypersensitivity>

## Vancomycin

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).

### Mechanism of action

- inhibits cell wall formation by binding to D-Ala-D-Ala moieties, preventing polymerization of peptidoglycans

### Mechanism of resistance

- alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits (normally D-alanyl-D-alanine) to which the antibiotic binds

### Adverse effects

- nephrotoxicity
- ototoxicity
- thrombophlebitis
- red man syndrome; occurs on rapid infusion of vancomycin

### Question 7 of 117

A 29-year-old lady comes to see you for advice having seen news of the recent Zika virus outbreak. She and her husband are planning on starting a family, but she has only arrived back from Brazil last week after a business trip. She has not experienced any fever or worrying symptoms, either during travel or since arrival back in the UK. What would be the most appropriate advice to give her?

[Start 5mg folic acid daily11%](#)[If no fever can become pregnant7%](#)[Need to check Zika virus serology before becoming pregnant21%](#)[Should avoid becoming pregnant for at least 2 weeks after travel13%](#)[Should avoid becoming pregnant for at least 8 weeks after travel48%](#)

The latest advice as per Public Health England is that women who are considering becoming pregnant should avoid becoming pregnant while travelling in an area with active Zika virus transmission, and for 8 weeks after their return.

Whilst folic acid is recommended to women trying for pregnancy, the usual dose is 400 micrograms daily and there is currently no recommendation to increase this after Zika exposure.



The test for Zika serology is only recommended for patients with a relevant travel history and current symptoms.

## **Zika virus**

Zika is a mosquito-borne infection caused by Zika virus, a member of the genus flavivirus and family Flaviviridae. It was first isolated from a monkey in the Zika forest in Uganda in 1947.

Transmission is usually via the bite of an infected Aedes mosquito, although a small number of cases of sexual transmission have been reported. There is increasing evidence of transmission via the placenta from mother to fetus.

The majority of people infected with Zika virus have no symptoms. For those with symptoms, Zika virus tends to cause a mild, short-lived (2 to 7 days) febrile disease. Signs and symptoms suggestive of Zika virus infection may include a combination of the following:

- fever
- rash
- arthralgia/arthritis
- conjunctivitis
- myalgia
- headache
- retro-orbital pain
- pruritus

Serious complications in adults are not common, although the virus has been associated with Guillain-Barre syndrome. Scientific consensus however has linked Zika with microcephaly and other congenital abnormalities, which has led the World Health Organisation (WHO) to declare a Public Health Emergency of International Concern (PHEIC).

## **Advice for travellers**

There is currently no vaccine or drug to prevent Zika infection. Prevention revolves around avoiding mosquito bites (Aedes mosquitoes usually bite during the day) by using mosquito repellent and cover up clothing. Pregnant women are advised to avoid non-essential travel to Zika prevalent areas until after pregnancy.

### Question 1 of 110

A 19-year-old man attends the Emergency department with a fever for the past one week. He notes that the fever comes on alternate days. He reports also a co-existing headache, but no other particular symptoms. Of note, he returned from Afghanistan two weeks ago. Examination reveals a temperature of 38.1°C, heart rate 89/min, blood pressure 123/78 mmHg, respiratory rate 17/min and oxygen saturations of 99%. There is no evidence of no neck stiffness, objective photophobia, jaundice or splenomegaly.

What is the most likely diagnosis?

[Chikungunya16%](#)[Zika virus9%](#)[Plasmodium vivax52%](#)[Plasmodium falciparum14%](#)[Dengue fever9%](#)

Fever in the returning traveller is a common presentation in the Emergency department. A knowledge of the areas travelled and incubation periods is essential to accurately diagnosing the potential infectious disease.

Chikungunya is a viral disease transmitted to humans via infected mosquitos. Fever and joint pain is the mos common presentation. The incubation period is 2-12 days.

Zika virus is currently not present in Afghanistan.

Dengue fever has a incubation period of 4-10 days.

This leaves plasmodium falciparum, which has a usual incubation of 7-14 days (but up to 3 months), and plasmodium vivax which has a typical incubation of 12-17 days (but reported up to 12 months) following exposure. Factors that point away from p. falciparum are the milder presentation and the much lower prevalence of it in Afghanistan (p. falciparum 5%, p. vivax 95%). Furthermore, fever due to malaria on alternate days, known as benign tertian malaria, is suggestive of either p. vivax or p. ovale. Comparatively, p. falciparum will typically cause more of a continuous fever.

### **Malaria: non-falciparum**

The most common cause of non-falciparum malaria is *Plasmodium vivax*, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases. *Plasmodium vivax* is often found in Central America and the Indian Subcontinent whilst *Plasmodium ovale* typically comes from Africa

Features

- general features of malaria: fever, headache, splenomegaly
- *Plasmodium vivax/ovale*: cyclical fever every 48 hours. *Plasmodium malariae*: cyclical fever every 72 hours
- *Plasmodium malariae*: is associated with nephrotic syndrome

Ovale and vivax malaria have a hypnozoite stage and may therefore relapse following treatment.

#### Treatment

- in areas which are known to be chloroquine-sensitive then WHO recommend either an artemisinin-based combination therapy (ACT) or chloroquine
- in areas which are known to be chloroquine-resistant an ACT should be used
- ACTs should be avoided in pregnant women
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse

#### Question 3 of 110

A 45-year-old male is brought into the emergency department by his partner. He is known to be HIV +ve and his partner reports good compliance with his medications since his diagnosis 4 years ago. A collateral history reveals persistent confusion over the past 3 weeks. His past medical history includes outpatient treatment 2 years ago for lymphogranuloma venereum and type 2 diabetes mellitus. On examination, the patient is not orientated in time or place. He scores 0/10 on the abbreviated mental test. Both heart sounds are present, include a mild early diastolic murmur. Neurological examination is difficult due to poor patient compliance but you note absent reflexes in both lower limbs, with an upgoing plantar on the left and withdrawn plantar on the right. You also note that he has erythematous soles on both feet. Blood tests and blood glucose are awaited. What is the most likely diagnosis?

[Subacute combined degeneration of the cord11%Motor neurone disease4%Neurosyphilis66%Hypoglycaemia and diabetic peripheral neuropathy5%HIV dementia and peripheral neuropathy13%](#)

A number of features suggest neurosyphilis from the history. Firstly, the likely aortic regurgitation on cardiovascular examination should make you suspicious of aortitis, of which syphilitic infection is a classic cause. He has had a range of sexually transmitted diseases. A painless red rash is also a classic sign of syphilis, particularly in palms of the hands or the soles of the feet. He also has a combined upgoing plantar with absent ankle jerks, which narrows the diagnosis to the classic five MRCP favourite of motor neurone disease, tabes dorsalis, subacute combined degeneration of the cord, Friedrich's ataxia and dual pathology of central and peripheral causes. There is little to suggest a genetic disorder presenting in his mid-40s or a vitamin B deficiency to account for SCDC. Neurosyphilis would be the most likely diagnosis.

## Syphilis

Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. Infection is characterised by primary, secondary and tertiary stages. The incubation period is between 9-90 days

### Primary features

- chancre - painless ulcer at the site of sexual contact
- local non-tender lymphadenopathy
- often not seen in women (the lesion may be on the cervix)

Secondary features - occurs 6-10 weeks after primary infection

- systemic symptoms: fevers, lymphadenopathy
- rash on trunk, palms and soles
- buccal 'snail track' ulcers (30%)
- condylomata lata



© Image used on license from [DermNet NZ](https://www.dermnetnz.org/)

Classical palm lesions of secondary syphilis



© Image used on license from [DermNet NZ](https://www.dermnet.nz/)



More generalised rash of secondary syphilis

Tertiary features

- gummas (granulomatous lesions of the skin and bones)
- ascending aortic aneurysms
- general paralysis of the insane
- tabes dorsalis
- Argyll-Robertson pupil

Features of congenital syphilis

- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- saddle nose
- deafness

### Question 1 of 107

A 44 year-old lady presented to the medical outpatient clinic with leg swelling which had progressively increased over the last 2 years. Her past medical history consisted only of a hospital admission for malaria as a child. She had grown up in urban Nigeria and moved to the United Kingdom 6 years ago to work as a teacher, but had been forced to stop working due to mobility problems. She was a non-smoker and did not drink alcohol.

On examination, her temperature was 36.5°C, heart rate 80 beats per minute, blood pressure 133/89 mmHg, respiratory rate 16 breaths per minute and oxygen saturations 98% on room air. Non-pitting leg swelling was apparent bilaterally extending proximally to the hips, with thickening of the overlying skin. Her chest was clear on auscultation and heart sounds were normal. The JVP was not elevated.

### Investigations:

Haemoglobin	138 g/L
White cell count	$7.0 \times 10^9/l$
Neutrophil count	$4.8 \times 10^9/l$
Lymphocyte count	$2.0 \times 10^9/l$
Eosinophil count	$0.1 \times 10^9/l$
Platelets	$246 \times 10^9/l$

Sodium	142 mmol/L
Potassium	4.3 mmol/L
Urea	6.0 mmol/L
Creatinine	84 mol/L
Alkaline phosphatase	40 IU/L
Alanine aminotransferase	32 IU/L
Gamma-glutyl transferase	23 IU/L
Bilirubin	16 mol/L
Albumin	41 g/L
Fasting plasma glucose	5.3 mmol/L

What is the most likely causative organism?

[\*Wuchereria bancrofti\*64%\*Brugia malayi\*12%\*Brugia timori\*8%\*Onchocerca volvulus\*11%\*Mansonella streptocerca\*5%](#)

This patient has presented with elephantiasis caused by chronic lymphatic inflammation and blockage in the lower limbs. The condition is caused by infiltration of the lymphatic system by filarial nematodes, which are transmitted by mosquitoes. *Wuchereria bancrofti*, *Brugia malayi*

and *Brugia timori* are all potential causative organisms, but *Wuchereria bancrofti* is by far the most common, accounting for 90% of cases. *Onchocerca volvulus* causes skin disease and river blindness, while *Mansonella streptocerca* causes skin disease alone.

## Helminths

### Nematodes (roundworms)

Worm	Notes	Treatment
	Larvae are present in soil and gain access to the body by penetrating the skin	
<i>Strongyloides stercoralis</i>	Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms	Ivermectin and -bendazoles are used
<i>Enterobius vermicularis</i> (pinworm)	Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	-bendazoles
<i>Ancylostoma duodenale</i> , <i>Necator americanus</i> (hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova Transmission by deer fly and mango fly	-bendazoles
<i>Loa loa</i>	Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae Typically develops after eating raw pork	Diethylcarbamazine
<i>Trichinella spiralis</i>	Features include fever, periorbital oedema and myositis (larvae encyst in muscle)	-bendazoles

Worm	Notes	Treatment
<i>Onchocerca volvulus</i>	Causes 'river blindness'. Spread by female blackflies Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria	Ivermectin <b>rIVER</b> blindness = <b>IVER</b> mectin
<i>Wuchereria bancrofti</i>	Transmission by female mosquito Causes blockage of lymphatics → elephantiasis Transmitted through ingestion of infective eggs.	Diethylcarbamazine
<i>Toxocara canis</i> (dog roundworm)	Features include visceral larva migrans and retinal granulomas VISCious dogs → blindness	Diethylcarbamazine
<i>Ascaris lumbricoides</i> (giant roundworm)	Eggs are visible in faeces May cause intestinal obstruction and occasional migrate to lung (Löffler's syndrome)	-bendazoles

### Cestodes (tapeworms)

Worm	Notes	Treatment
<i>Echinococcus granulosus</i>	Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers.	-bendazoles
<i>Taenia solium</i>	Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal) Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
<i>Fasciola hepatica</i> (the liver fluke)	May cause biliary obstruction	Triclabendazole

### Trematodes (flukes)

Worm	Notes	Treatment
<i>Schistosoma haematobium</i>	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
<i>Paragonimus westermani</i>	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs	Praziquantel



Worm	Notes	Treatment
	Caused by undercooked fish	
<i>Clonorchis sinensis</i>	Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	Praziquantel

Question 2 of 107

A 22-year-old lady, with lupus and antiphospholipid syndrome, presented to the Rheumatology clinic with sharp chest pain across her right side.

This pain had started 3 days prior to presentation. She had some shortness of breath. She reported that she has a vesicular rash that had started 1 day ago over that area.

She weighs 65KG

Her medications include:

Methotrexate 20mg once weekly

Prednisolone 30mg once a day

Aspirin 75mg once a day

Folic Acid 5mg once a day

She was admitted to the rheumatology ward and underwent a CT pulmonary angiography which showed no pulmonary emboli, but widespread bilateral changes of subsolid nodules and ground-glass opacification.

Her shortness of breath started to get worse and her observations were taken.

Observations:

Temperature 39.1°C

Blood pressure 107/55mmHg

Heart rate 122beats/min

Oxygen saturation 88% on air

What is the best treatment for her likely diagnosis?

[Treat with dalteparin subcutaneously6%](#)[Treat with intravenous amoxicillin and oral clarithromycin13%](#)[Treat with intravenous amoxicillin5%](#)[Treat with aciclovir intravenous68%](#)[Treat with aciclovir orally8%](#)

The most likely diagnosis for this immunocompromised lady with sharp pain and a vesicular rash is varicella zoster chickenpox. She is systemically unwell with it and has widespread pulmonary changes that are consistent with varicella pneumonitis.

The treatment of choice in an immunocompromised host with varicella zoster is intravenous aciclovir.

Answers 1,2 and 3 would not treat the varicella zoster infection.

<https://www.britishinfection.org/files/9114/1617/4223/jeffery08VZV0.pdf>

## **Chickenpox**

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion

Chickenpox is highly infectious

- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared\*
- incubation period = 10-21 days

Clinical features (tend to be more severe in older children/adults)

- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management is supportive

- keep cool, trim nails
- calamine lotion
- school exclusion\*: children should be kept away from school for at least 5 days from onset of rash (and not developing new lesions)

- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered

A common complication is secondary bacterial infection of the lesions. Rare complications include

- pneumonia
- encephalitis (cerebellar involvement may be seen)
- disseminated haemorrhagic chickenpox
- arthritis, nephritis and pancreatitis may very rarely be seen



© Image used on license from [Radiopaedia](#)

Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

\*the official advice regarding school exclusion for chickenpox has gone back and forth over recent years. In September 2017 Public Health England advocated the 5 day rule:

*Children should be kept away from school for at least 5 days from onset of rash (and not developing new lesions). It is not necessary for all the spots to have healed or crusted over before return to school as the risk of transmission to other children after 5 days is minimal.*

<https://www.gov.uk/government/publications/health-protection-in-schools-and-other-childcare-facilities/chapter-9-managing-specific-infectious-diseases#chicken-pox-shingles>

Question 3 of 107

A 26-year-old woman presents to the emergency department with right upper quadrant pain which is worse when she takes a deep breath in. Her symptoms started three days earlier and have been progressively getting worse. She has no past medical history and takes no medications apart from the oral contraceptive pill and paracetamol to help control the pain. She has also noticed an increase in vaginal discharge over the last two weeks and has noticed an unpleasant smell with it. She works in an investment bank. On examination, she has right upper quadrant tenderness, but the abdomen is soft and no organomegaly is noticed. Abdominal ultrasound demonstrates the presence of gallstones in the gallbladder but is otherwise normal. What treatment is most likely to resolve the cause of her underlying problem?

[Cholecystectomy16%](#) [Trimethoprim10%](#) [Antiviral treatment6%](#) [Antiretroviral treatment8%](#) [Ceftriaxone60%](#)

The correct answer is ceftriaxone. This woman has unfortunately developed Fitz-Hugh-Curtis syndrome following pelvic inflammatory diseases. The key aspects are RUQ pain worse with breathing; symptomatic of peri-hepatic adhesions. This combined with vaginal discharge are highly suggestive of Fitz-Hugh-Curtis syndrome, which can be treated with antibiotics. Cholecystectomy would be appropriate management if the US had found evidence of cholecystitis. Trimethoprim would be appropriate if there was evidence of urinary symptoms, whilst there is no evidence to suggest that this is an AIDS-defining illness needing antiretroviral treatment. Antiviral treatment would imply viral hepatitis, but there is no clear evidence of hepatitis.

## **Gonorrhoea**

Gonorrhoea is caused by the Gram negative diplococcus *Neisseria gonorrhoeae*. Acute infection

can occur on any mucous membrane surface, typically genitourinary but also rectum and pharynx. The incubation period of gonorrhoea is 2-5 days

### Features

- males: urethral discharge, dysuria
- females: cervicitis e.g. leading to vaginal discharge
- rectal and pharyngeal infection is usually asymptomatic

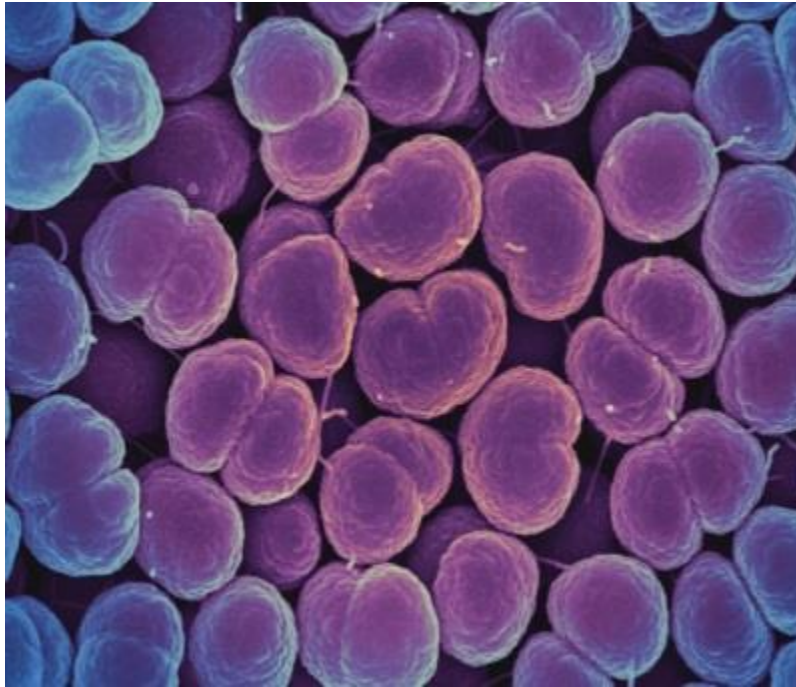
### Microbiology

- immunisation is not possible and reinfection is common due to antigen variation of type IV pili (proteins which adhere to surfaces) and Opa proteins (surface proteins which bind to receptors on immune cells)

Local complications that may develop include urethral strictures, epididymitis and salpingitis (hence may lead to infertility). Disseminated infection may occur - see below

### Management

- ciprofloxacin used to be the treatment of choice. However, there is increased resistance to ciprofloxacin and therefore cephalosporins are now used
- the 2011 British Society for Sexual Health and HIV (BASHH) guidelines recommend ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g oral as a single dose. The azithromycin is thought to act synergistically with ceftriaxone and is also useful for eradicating any co-existent Chlamydia infections. This combination can be used in pregnant women as well
- if ceftriaxone is refused or contraindicated other options include cefixime 400mg PO (single dose)



Colorized scanning electron micrograph of *Neisseria gonorrhoeae*. Credit: NIAID

Disseminated gonococcal infection (DGI) and gonococcal arthritis may also occur, with gonococcal infection being the most common cause of septic arthritis in young adults. The pathophysiology of DGI is not fully understood but is thought to be due to haematogenous spread from mucosal infection (e.g. Asymptomatic genital infection). Initially there may be a classic triad of symptoms: tenosynovitis, migratory polyarthritits and dermatitis. Later complications include septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome)

Key features of disseminated gonococcal infection

- tenosynovitis
- migratory polyarthritits
- dermatitis (lesions can be maculopapular or vesicular)

Question 4 of 107

A 17-year-old man who has recently come to the UK from Rwanda is admitted to hospital. His friend describes him complaining of a headache and fever for the past four days. Further history reveals that he is very lethargic with a dry cough and generalised myalgia. The patient also describes passing some dark urine this morning. He has no past medical history of note. On examination his pulse is 110/min, temperature 38.1°C, oxygen saturations 98% on room air and

blood pressure 110/68 mmHg, His sclera are jaundiced and there is enlargement of the liver and spleen. Bloods show the following:

Na<sup>+</sup> 142 mmol/l  
K<sup>+</sup> 4.8 mmol/l  
Urea 12.3 mmol/l  
Creatinine 144 µmol/l

What is the most likely diagnosis?

[Typhoid7%Dengue fever18%African trypanosomiasis15%Malaria42%Leishmaniasis17%](#)

This patient clearly has an infective process so much of the data (headache, fever, myalgia, vital signs) can be discarded as being common to all the answers.

We're now left with more concrete findings: jaundice, hepatosplenomegaly and a raised creatinine.

Now we take one of these findings, hepatosplenomegaly and consider the differential diagnosis:

Causes of hepatosplenomegaly

- chronic liver disease with portal hypertension
- infections: glandular fever, malaria, hepatitis
- lymphoproliferative disorders
- myeloproliferative disorders e.g. chronic myeloid leukaemia
- amyloidosis

This suggests that malaria is the most likely diagnosis. Jaundice and a raised creatinine are consistent with this.

## **Malaria: Falciparum**

Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 °C

- severe anaemia
- complications as below

### Complications

- cerebral malaria: seizures, coma
- acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
- acute respiratory distress syndrome (ARDS)
- hypoglycaemia
- disseminated intravascular coagulation (DIC)

### Uncomplicated falciparum malaria

- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

### Severe falciparum malaria

- a parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

### Question 5 of 107

A 32-year-old lady presented after returning from Nigeria 3 weeks ago to her GP complaining of feeling feverish and pain in her joints making walking difficult. She denied any rash, or headaches however she has been very drowsy and lethargic in the past week. She spent a week in Nigeria and visited her relatives both in urban and rural areas. She has been taking her malaria prophylaxis tablets. She denies being sexually active for the past year. Her GP sent off three malaria screens which were negative.

Two months later she represents to the emergency department following a seizure and is found to



be confused and disorientated. She is irritable, and you notice her hand is trembling. Her sister says she has lost her appetite and weight and has been behaving strangely in the past month. She spends most of her time in bed during the day complaining of a headache and has become withdrawn. On examination, there is hypertonia in her limbs, with hyperreflexia, but the rest of examination is difficult as she is uncooperative.

Investigations:

Na+	140mmol/l
K+	4.3 mmol/l
Urea	5.3 mmol/l
Creatinine	85 µmol/l
Serum bilirubin	15 µmol/l
Serum alkaline phosphatase	85 IU/l
Serum aspartate aminotransferase	19 IU/l
Serum Albumin	25 g/l
C Reactive protein (CRP)	25 mg/l
Erythrocyte Sedimentation Rate (ESR)	75 mm/hr
Haemoglobin	96 g/l
White cell count	10.2 x 10 <sup>9</sup> /L
Neutrophils	8.9 x 10 <sup>9</sup> /L
Eosinophilia	0.1 x10 <sup>9</sup> /L
Lymphocytes	1.8 x 10 <sup>9</sup> /L
Platelets	140 x 10 <sup>9</sup> /L
INR	1.0

What is the likely causative organism?

[\*Plasmodium vivax\*8%\*Borrelia burgdorferi\*11%\*Trypanosoma gambiense\*45%\*Trypanosoma rhodesiense\*19%\*Trypanosoma cruzi\*16%](#)

This lady of African background presents initially with fever after travelling from Nigeria and goes on to develop chronic symptoms of daytime somnolence, continuous headaches and behavioural changes. These symptoms suggest African Sleeping Sickness or African Trypanosomiasis. *Trypanosoma gambiense* is more common than *Trypanosoma rhodesiense* in patients from West Africa, such as Nigeria.

Early stages of the disease tends to present about 3 weeks after being bitten by an infected tsetse fly. Symptoms include fevers, arthralgia, lethargy, drowsiness. Late stages include behavioural and mood changes, headache and the pathognomonic daytime somnolence with nocturnal insomnia.

*Borrelia burgdorferi* is transmitted by ticks (*Ixodes* spp.) and causes Lyme disease. They occur in the USA, northern and central European countries, and temperate forested areas of Asia.

*Plasmodium vivax* is one species of Plasmodium, the parasite that causes malaria. It is spread by infected mosquitoes. It is an important differential of fever in the returning traveller, however as the initial malaria screens were negative, and the central nervous system symptoms in the late stages are not consistent with a malarial infection.

*Trypanosoma cruzi* is responsible for American Trypanosomiasis (or Chagas' disease). It is transmitted by contamination with infected faeces of assassin bugs (reduviid bugs). It is found in South America and the south USA. Chronic infection can lead to chronic congestive heart failure, megaesophagus and megacolon.

## Trypanosomiasis

Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly. *Trypanosoma rhodesiense* tends to follow a more acute course. Clinical features include:

- Trypanosoma chancre - painless subcutaneous nodule at site of infection
- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis

## Management

- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract

- myocarditis may lead to dilated cardiomyopathy (with apical atrophy) and arrhythmias

- gastrointestinal features includes megaoesophagus and megacolon causing dysphagia and constipation

## Management

- treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure

## Question 6 of 107

A 36 year old male Intravenous drug user presents to genito-urinary clinic. He was diagnosed with HIV 3 years ago after presenting with tuberculosis (TB). He was treated for TB for 6 months. He is now on third line anti-retroviral therapy for previous virological failure and co-trimoxazole. His most recent CD4 count was 104, and his viral load was 3,000 copies/ml.

He complains of weakness on his left side, and deterioration in vision, getting worse for four weeks. He has a moderately severe headache. On examination his visual acuity is 3/60 in his left eye and 6/6 in his right eye. He has weakness, in his left arm and leg, brisk reflexes and mildly increased tone.

He is immediately admitted.

A CT scan shows several ring enhancing lesions in his right cerebral hemispheres and one on the left cerebral hemisphere.

On ophthalmological review he has a large area of retinal necrosis in his left eye.

What is the diagnosis?

[CNS lymphoma 7%](#) [Cerebral toxoplasmosis 78%](#) [Cerebral TB 7%](#) [Cerebral abscesses 4%](#) [CNS Kaposi sarcoma 5%](#)

The most important three differential diagnosis for a ring-enhancing lesion in an HIV patient is CNS lymphoma, TB and Toxoplasmosis.

In this case the retinal necrosis is characteristic of ophthalmic toxoplasmosis. Multiple lesion also favour toxoplasmosis. His poor compliance with HIV treatment (as indicated by the low CD4 count and the high viral load) suggest his compliance with co-trimoxazole is also poor.

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

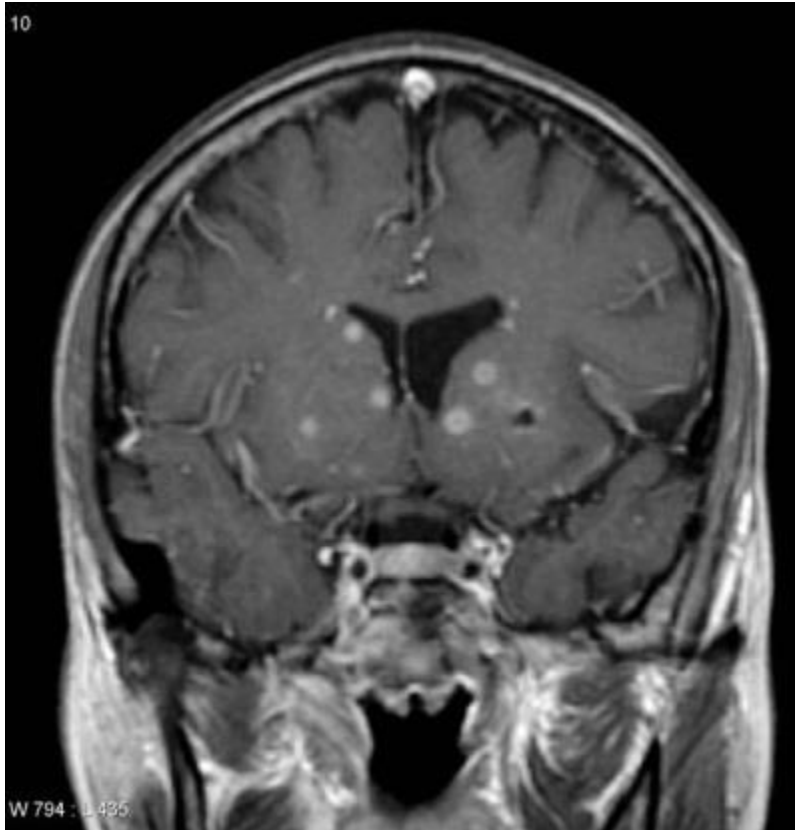
- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



© Image used on license from [Radiopaedia](#)

Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



© Image used on license from [Radiopaedia](#)

Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
Thallium SPECT negative	Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 2 of 100

A 39-year-old female with end-stage renal failure secondary to IgA nephropathy is admitted to hospital. She was discharged 3 days earlier following an admission due to collapse in the context of hyperkalaemia (Potassium 7.8 mmol/l). She has been transferred to the medical assessment unit having developed rigors on dialysis earlier today.

Bloods taken at the end of dialysis reveal:

White cell count                      15.2 \*10<sup>9</sup>/l



Sodium	134 mmol/l
Potassium	2.1 mmol/l
Urea	10.6 mmol/l
Creatinine	400 µmol/l
C-reactive protein (CRP)	119 mg/dL

What is the immediate priority in her management?

[Replace potassium \(K<sup>+</sup>\)33%](#)[Replace magnesium \(Mg<sup>2+</sup>\)15%](#)[Intravenous antibiotics37%](#)[Intravenous calcium gluconate11%](#)[Insulin/dextrose infusion4%](#)

The patient is septic and infection is her most imminent threat. Post-dialysis bloods are often misleading in terms of electrolytes as it takes 30 minutes for intracellular and extracellular compartments to equilibrate. Assuming that the patient's pre-dialysis bloods showed a high-normal K<sup>+</sup> (which would fit with her recent hyperkalaemia presentation) then her total body K<sup>+</sup> will be much higher than the post-dialysis sample suggests. The bloods should be repeated to confirm this but over-zealous correction of K<sup>+</sup> in this situation can be dangerous.

Magnesium is important to correct in the presence of hypokalaemia, however, we do not think this patient genuinely has low potassium. Intravenous calcium gluconate and insulin/dextrose infusion are both treatments for hyperkalaemia and therefore are not appropriate.

## Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection. Sepsis is increasingly recognised as an important cause of mortality in the UK and there has been increasing efforts recently to improve the care of patients who present with sepsis.

How sepsis is classified has changed in recent years - the Surviving Sepsis Guidelines were updated in 2017.

The new guidelines recognise the following terms:

- **sepsis:** life-threatening organ dysfunction caused by a dysregulated host response to infection
- **septic shock:** a more severe form of sepsis, technically defined as *'in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone'*\*

The old category of severe sepsis is no longer used.

The term 'systemic inflammatory response syndrome (SIRS)' has also fallen out of favour. Adult patients outside of ICU with suspected infection are identified as being at heightened risk of mortality if they have quickSOFA (qSOFA) score meeting  $\geq 2$  of the following criteria: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100mmHg or less

## Management

NICE released their own guidelines in 2016. These focussed on the risk stratification and management of patients with suspected.

For risk stratification NICE recommend using the following criteria:

Red flag criteria	Amber flag criteria
<ul style="list-style-type: none"><li>• Responds only to voice or pain/ unresponsive</li><li>• Acute confusional state</li><li>• Systolic B.P <math>\leq 90</math> mmHg (or drop <math>&gt;40</math> from normal)</li><li>• Heart rate <math>&gt; 130</math> per minute</li><li>• Respiratory rate <math>\geq 25</math> per minute</li><li>• Needs oxygen to keep SpO<sub>2</sub> <math>\geq 92\%</math></li><li>• Non-blanching rash, mottled/ ashen/ cyanotic</li><li>• Not passed urine in last 18 h/ UO <math>&lt; 0.5</math> ml/kg/hr</li><li>• Lactate <math>\geq 2</math> mmol/l</li><li>• Recent chemotherapy</li></ul>	<ul style="list-style-type: none"><li>• Relatives concerned about mental status</li><li>• Acute deterioration in functional ability</li><li>• Immunosuppressed</li><li>• Trauma/ surgery/ procedure in last 6 weeks</li><li>• Respiratory rate 21-24</li><li>• Systolic B.P 91-100 mmHg</li><li>• Heart rate 91-130 OR new dysrhythmia</li><li>• Not passed urine in last 12-18 hours</li><li>• Temperature <math>&lt; 36^{\circ}\text{C}</math></li><li>• Clinical signs of wound, device or skin infection</li></ul>

Clearly the underlying cause of the patients sepsis needs to be identified and treated and the patient supported regardless of the cause or severity. If however any of the red flags are present the 'sepsis six' should be started straight away:

1. Administer oxygen: Aim to keep saturations  $> 94\%$  (88-92% if at risk of CO<sub>2</sub> retention e.g. COPD)
2. Take blood cultures
3. Give broad spectrum antibiotics
4. Give intravenous fluid challenges: NICE recommend a bolus of 500ml crystalloid over less than 15 minutes
5. Measure serum lactate
6. Measure accurate hourly urine output

\*these patients can be clinically identified by a vasopressor requirement to maintain a MAP  $\geq$  65mmHg and serum lactate  $>2$ mmol/L in the absence of hypovolemia

#### Question 2 of 100

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- Responds only to voice or pain/ unresponsive
- Acute confusional state
- Systolic B.P  $\leq 90$  mmHg (or drop  $>40$  from normal)
- Heart rate  $> 130$  per minute
- Respiratory rate  $\geq 25$  per minute
- Needs oxygen to keep SpO<sub>2</sub>  $\geq 92\%$
- Non-blanching rash, mottled/ ashen/ cyanotic
- Not passed urine in last 18 h/ UO  $< 0.5$  ml/kg/hr
- Lactate  $\geq 2$  mmol/l

### Amber flag criteria

- Relatives concerned about mental status
- Acute deterioration in functional ability
- Immunosuppressed
- Trauma/ surgery/ procedure in last 6 weeks
- Respiratory rate 21-24
- Systolic B.P 91-100 mmHg
- Heart rate 91-130 OR new dysrhythmia
- Not passed urine in last 12-18 hours
- Temperature  $< 36^{\circ}\text{C}$
- Clinical signs of wound, device or skin

### **Red flag criteria**

- Recent chemotherapy

### **Amber flag criteria**

infection

Clearly the underlying cause of the patient's sepsis needs to be identified and treated and the patient supported regardless of the cause or severity. If however any of the red flags are present the 'sepsis six' should be started straight away:

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- 3. Give broad spectrum antibiotics
- 4. Give intravenous fluid challenges: NICE recommend a bolus of 500ml crystalloid over less than 15 minutes
- 5. Measure serum lactate
- 6. Measure accurate hourly urine output

\*these patients can be clinically identified by a vasopressor requirement to maintain a MAP  $\geq 65$ mmHg and serum lactate  $> 2$ mmol/L in the absence of hypovolemia

### Question 1 of 100

A 40-year-old yoga teacher is reviewed in respiratory clinic following a recent presentation to the emergency department with fever and lethargy. The patient describes a six month history of night sweats, weight loss and progressive reduced exercise capacity that has left him unable to work. During a short admission to hospital he was diagnosed with active pulmonary tuberculosis on the basis of a suggestive chest x-ray and sputum microscopy. He was initiated on standard combination therapy for tuberculosis and discharged for outpatient follow-up.

At clinic, the patient denies feeling any significant improvement in his symptoms. A detailed social history is taken and the patient reports no risk factors for blood-borne viral infections. However, he does report spending 9 months in rural India three years previously as part of his yoga study.

Examination shows the patient to be noticeably cachexic, with a further 3 kg weight loss recorded compared to at the time of hospital admission.

Please see below for results of investigations requested while the patient was an inpatient. Following review of the results, the need for intravenous treatment is explained to the patient.

HIV serum antibody not detected

HIV serum RNA not detected

Phenotypic indirect drug susceptibility testing: rifampicin (resistant); ofloxacin (sensitive); moxifloxacin (sensitive); isoniazid (resistant); amikacin (sensitive); kanamycin (sensitive).

What is the appropriate duration of intravenous treatment for this patient?

[9-12 months26% 18-24 months35% 1-2 months7% 6-8 months18% 3-6 months14%](#)

The patient has multi-drug resistance TB, presumably contracted during his time spent living in India, where resistant TB strains are common. Multi-drug resistant TB should be treated with an injectable agent such as amikacin, kanamycin or capreomycin, in combination with a fluoroquinolone and at least three other agents.

Ideally the injectable agent is administered daily for the first 6-8 months, forming an intensive phase of treatment, with other drugs then continued for a total of 18-24 months. In practice, unwanted effects may lead to intravenous therapy being discontinued early.

Millard J, Ugarte-Gil C, Moore D. Multidrug resistant tuberculosis. BMJ 2015;350:h882.

## **Tuberculosis: management**

Stop medication if LFT's > 5 times normal limit

Immune reconstitution disease

- occurs typically 3-6 weeks after starting treatment
- often presents with enlarging lymph nodes

Question 3 of 100

A 72-year-old male diabetic is admitted to the hospital via the Emergency Department with severe cellulitis of his right arm. He is hypertensive and also suffers from coronary artery disease.

On examination he is febrile, with a temperature of 38.5°C. His pulse is 112 bpm and his blood pressure is 150/95 mmHg.

His right arm is grossly swollen and tender, with marked erythema and discharge of small amounts of pus.

Lab reports reveal:

Hb 90 g/l  
MCV 71 fl  
WBC  $23 \times 10^9/l$   
Plt  $500 \times 10^9/l$   
Urea 9.2 mmol/l  
Creatinine 145  $\mu\text{mol/l}$

Urine examination reveals proteinuria 1+ and glycosuria 2+

Preliminary blood cultures post admission reveal the growth of MRSA.

Which of the following would be the most appropriate antibiotic for this patient?

[IV Vancomycin 62% IV Flucloxacillin 8% IV Linezolid 20% IV Rifampicin 5% IV Gentamicin 5%](#)

IV Vancomycin is the treatment of choice for MRSA septicaemia. The renal function is slightly deranged here so the dosing will need to be adjusted accordingly.

## MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first organisms which highlighted the dangers of hospital-acquired infections.

Who should be screened for MRSA?

- all patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded)
- from 2011 all emergency admissions will be screened

How should a patient be screened for MRSA?

- nasal swab and skin lesions or wounds
- the swab should be wiped around the inside rim of a patient's nose for 5 seconds

- the microbiology form must be labelled 'MRSA screen'

#### Suppression of MRSA from a carrier once identified

- nose: mupirocin 2% in white soft paraffin, tds for 5 days
- skin: chlorhexidine gluconate, od for 5 days. Apply all over but particularly to the axilla, groin and perineum

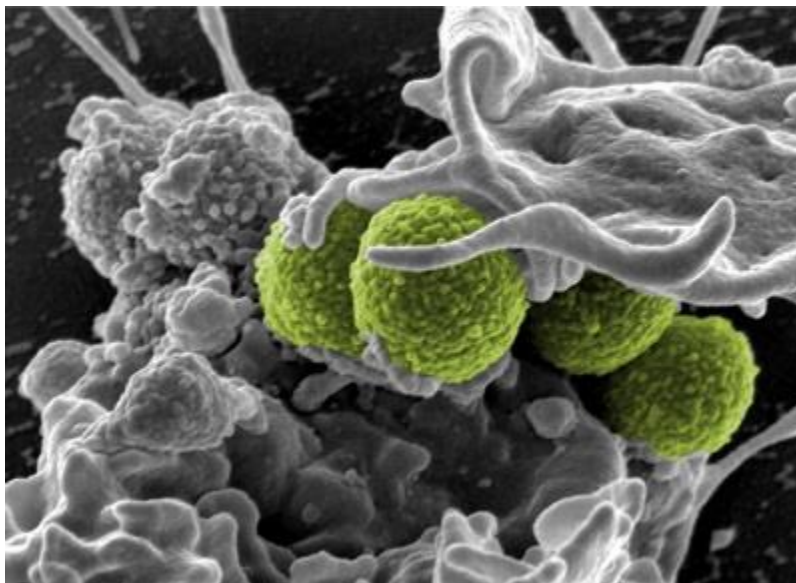
The following antibiotics are commonly used in the treatment of MRSA infections:

- vancomycin
- teicoplanin
- linezolid

Some strains may be sensitive to the antibiotics listed below but they should not generally be used alone because resistance may develop:

- rifampicin
- macrolides
- tetracyclines
- aminoglycosides
- clindamycin

Relatively new antibiotics such as linezolid, quinupristin/dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases







Interaction of MRSA (green bacteria) with a human white cell. The bacteria shown is strain MRSA252, a leading cause of hospital-associated infections in the United States and United Kingdom. Credit: NIAID

#### Question 4 of 100

A 25-year-old woman returns from a holiday in Thailand with diarrhoea. She has no past medical history and takes no regular tablets apart from the oral contraceptive pill. She has no allergies apart from peanuts. She has been suffering from diarrhoea for three days with mild abdominal cramps which started five days after returning from her trip. There has been a small amount of blood in her stool. Her observations are within normal range. She has no postural symptoms. Stool samples are requested and sent to the microbiology lab. What is the most appropriate treatment?

[Ciprofloxacin35%](#) [Tetracycline5%](#) [Oral rehydration solution34%](#) [Metronidazole23%](#) [Co-amoxiclav4%](#)

The correct answer is oral rehydration solution. Empirical antibiotics are only indicated if systemically unwell, immunosuppressed or if elderly, even if the patient has bloody diarrhoea. Ciprofloxacin is used to treat *Salmonella*, *Shigella* and *Campylobacter*, tetracycline can be used for cholera, metronidazole in parasitic infections or other bowel problems, and finally, co-amoxiclav is seldom used in enteric infections.

### Gastroenteritis

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The most common cause is *Escherichia coli*

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

### Stereotypical histories

<b>Infection</b>	<b>Typical presentation</b>
<b><i>Escherichia coli</i></b>	Common amongst travellers Watery stools Abdominal cramps and nausea
<b>Giardiasis</b>	Prolonged, non-bloody diarrhoea
<b>Cholera</b>	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers
<b><i>Shigella</i></b>	Bloody diarrhoea Vomiting and abdominal pain
<b><i>Staphylococcus aureus</i></b>	Severe vomiting Short incubation period
<b><i>Campylobacter</i></b>	A flu-like prodrome is usually followed by crampy abdominal pains, fever and diarrhoea which may be bloody  Complications include Guillain-Barre syndrome Two types of illness are seen
<b><i>Bacillus cereus</i></b>	<ul style="list-style-type: none"> <li>• vomiting within 6 hours, stereotypically due to rice</li> <li>• diarrhoeal illness occurring after 6 hours</li> </ul>
<b>Amoebiasis</b>	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks

#### Incubation period

- 1-6 hrs: *Staphylococcus aureus*, *Bacillus cereus*\*
- 12-48 hrs: *Salmonella*, *Escherichia coli*
- 48-72 hrs: *Shigella*, *Campylobacter*
- > 7 days: Giardiasis, Amoebiasis

\*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

#### Question 5 of 100

Mrs Stevens is a 60-year-old lady with pulmonary fibrosis secondary to dermatomyositis. She returns to your clinic seven weeks after being commenced on high dose steroids due to disease progression. During the review Mrs Stevens describes increasing shortness of breath, which is worse when she exerts herself. She has not noticed any fever and has not lost any weight. She

has a chronic cough productive of white sputum. This remains stable.

On examination she looks comfortable at rest and auscultation of her chest is surprisingly clear. At rest her oxygen Sats are 97%. You ask her to walk to the end of the corridor and back. You notice that on returning her Sats have fallen to 82%. You request an urgent chest radiograph, which is reported as showing bilateral patchy infiltrates.

What is the most appropriate management option?

[Fluconazole7% Ambisome8% Co-trimoxazole71% Ribavirin5% Stop steroids9%](#)

The patient has PCP pneumonia, caused by *Pneumocystis jirovecii* - a yeast-like fungus which is an opportunistic pathogen. The treatment for this is co-trimoxazole.

All patients with dermatomyositis or polymyositis with pulmonary fibrosis who are treated with glucocorticoids are advised to receive PCP prophylaxis with co-trimoxazole. Stopping steroids would not be appropriate in this scenario.

It is important to note that not all patients taking glucocorticoids for rheumatological conditions require PCP prophylaxis. However, there is evidence that in non-HIV cohorts, the greatest risk for developing PCP is glucocorticoid use and deficiencies in innate and acquired immune components. Therefore, although there are currently no formal guidelines it is recommended that if an individual satisfies both these criteria in rheumatological conditions, they should be considered for PCP prophylaxis.

For example the following all should be considered for prophylaxis:

- A patient on the equivalent of 20 mg prednisolone or greater for one month plus the concomitant use of another immunosuppressive drug
- Dermatomyositis on high dose prednisolone for greater than one month and pulmonary fibrosis
- Allogenic or autogenic stem cell transplant or solid organ transplantation

Further reading can be found at:

<http://www.pneumon.org/assets/files/844/file483317.pdf>

**HIV: *Pneumocystis jiroveci* pneumonia**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count  $< 200/\text{mm}^3$  should receive PCP prophylaxis

#### Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

#### Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

#### Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if  $\text{pO}_2 < 9.3\text{kPa}$  then steroids reduce risk of respiratory failure by 50% and death by a third)



© Image used on license from [Radiopaedia](#)

CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

#### Question 1 of 95

A 45-year-old man is urgently referred to dermatology clinic by his general practitioner after presenting with erythema migrans on his left calf. The patient was very concerned about the possibility that he had contracted Lyme disease following his recent walking holiday in the Scottish highlands.

The patient reported returning from his holiday 2 weeks ago and first noticed the rash within the last 24 hours. The patient reported that he had undertaken long walks in the countryside wearing shorts but that he had not noticed any ticks becoming attached to his body during his holiday. Aside from the rash on his leg (described below) the patient reported no other symptoms at the present time or during recent weeks. In particular, the patient denied any symptoms involving the central or peripheral nervous systems.

The patient was in generally good physical health and his only past medical history was

hypertension treated with ramipril by his GP. The patient had no known allergies to any medications.

Examination of the patient's left leg demonstrated a circular erythematous rash 15 cm in diameter. The rash demonstrated an appearance typical for erythema migrans, featuring a central spot surrounded by a ring of clear skin and an outer ring of erythema. The patient reported that the area covered by the rash had expanded significantly in the 24 hours since he had first noticed it. A detailed examination of the remaining surface of the patient's skin did not identify any other significant rashes. Examination of the peripheral and central nervous system did not demonstrate any signs of focal neurology. Examination of the cardiovascular, respiratory and abdominal systems was unremarkable. There was no evidence of palpable lymphadenopathy.

What is the appropriate management of this patient's erythema migrans?

[Serological testing for pathogenic \*Borrelia\* species21% Treat with doxycycline for 14 days56% No further investigation or treatment required due to absence of history of tick bite5% Review patient in two weeks and arrange serological tests if onset of symptoms or signs of Lyme borreliosis8% Review patient in two weeks and treat with doxycycline if onset of symptoms or signs of Lyme borreliosis10%](#)

Lyme borreliosis is the commonest tick-borne infection in the northern hemisphere. It is relatively rare in the UK, with risk being greatest in rural forested areas such as the Scottish highlands, New Forest and Lake District. The illness is caused by pathogenic *Borrelia* species, members of the spirochete phylum.

Clinical features of Lyme borreliosis include erythema migrans in 90% of symptomatic individuals, which tends to occur 2-40 days following exposure. Erythema migrans has the classical appearance described in the question but may be homogeneous in the early phase and can be confused for cellulitis or a simple insect bite. Rarely, a non-specific febrile illness without rash can occur. Neurological involvement consisting of meningitis or cranial nerve palsy can occur in early infection.

Erythema migrans is a clinical diagnosis and does not require serological confirmation. Therefore, the patient should be treated immediately with a 2-3 week course of oral doxycycline or amoxicillin, even in the absence of a history of tick attachment. Early treatment of erythema migrans is associated with a good clinical outcome and it would be inappropriate to delay treatment until the onset of other symptoms.

Serological testing should be reserved for individuals in which there is diagnostic uncertainty, neurological symptoms or those who are immunocompromised. Individuals presenting following a tick bite should not be treated or undergo investigation in the absence of erythema migrans or other symptoms of Lyme borreliosis.

Duncan C, Carle G, Seaton R. Tick bite and early Lyme borreliosis. *BMJ* 2012;344:e3124.

## Lyme disease

Lyme disease is caused by the spirochaete *Borrelia burgdorferi* and is spread by ticks

### Features

- early: erythema chronicum migrans + systemic features (fever, arthralgia)
- CVS: heart block, myocarditis
- neuro: cranial nerve palsies, meningitis

### Investigation

- serology: antibodies to *Borrelia burgdorferi*. These can take 3-8 weeks before they are detectable

### Management

- doxycycline if early disease. Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
- ceftriaxone if disseminated disease
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

### Question 2 of 95

A 23-year-old white Caucasian left-handed male presents with a 24-hour history of slurred speech. He is a 'frequent flyer' in the Emergency Department with repeated admissions and known to be a user of intravenous drugs and alcohol. His past medical history includes depression and previously treated in adolescence for functional neurological symptoms. He denies having had a drink for the past 2 weeks but used intravenous cocaine yesterday.

On examination, he is obviously unkempt and has a lack of prominent veins. There is an old abscess scar over his right femoral crease. His speech is markedly slurred but he remains orientated to time and place. You also note a significant loss of forehead creasing and facial weakness on both sides of his face with normal facial sensation. In addition, his power is 4-/5 in shoulder

abduction, shoulder adduction, hip flexion and hip extension, with 5/5 power on all other movements. Reflexes were present in biceps, supinator, patella and ankle, with absent triceps reflex. Both plantar reflexes were downgoing. Sensation to cotton wool, proprioception and pinprick was normal, with the patient reporting no pain.

What is the most likely diagnosis?

[Heavy metal intoxication19%](#)[Guillain Barre syndrome6%](#)[Botulism58%](#)[Chronic inflammatory demyelinating polyneuropathy \(CIDP\)11%](#)[Myasthenia gravis5%](#)

The patient has presented with bilateral cranial neuropathies and symmetrical proximal weakness, in the context of intravenous drug use. The descending pattern of weakness is atypical for Guillain-Barre syndrome. The time course of within 8 weeks also rules out CIDP. Myasthenia gravis is a possibility but there is no suggestion of fatigability. The distinction between heavy metal intoxication and botulism is difficult: intravenous drug users, particularly those sourcing from Eastern Europe, who have been known to present with manganese poisoning due to dirty constituents. Clinical features of course depend on the precise metal involved but acute poisoning typically includes encephalopathy, gastrointestinal upset and myalgia in addition to peripheral neuropathy. Significant sensory neuropathy causing neuropathic pain is commonly prominent. In the case of this patient, with bilateral cranial neuropathies and symmetrical proximal weakness, in the context of intravenous drug use, makes botulism most likely. Treatment is with antitoxin, removal of the original source of infection in addition to close monitoring of respiratory function.

## **Botulism**

### *Clostridium botulinum*

- gram positive anaerobic bacillus
- 7 serotypes A-G
- produces botulinum toxin, a neurotoxin which irreversibly blocks the release of acetylcholine
- may result from eating contaminated food (e.g. tinned)
- neurotoxin often affects bulbar muscles and autonomic nervous system

### Features

- patient usually fully conscious with no sensory disturbance
- flaccid paralysis
- diplopia
- ataxia



- bulbar palsy

Treatment with antitoxin is only effective if given early - once toxin has bound its actions cannot be reversed

Therapeutic uses of botulinum toxin

- strabismus
- dystonias: torticollis, blepharospasm
- hyperhidrosis
- cosmetic: Botox: serotype A of botulinum toxin used

Question 3 of 95

A 37-year-old man is referred to the medical outpatient clinic. He was born in Brazil but has been in the UK since university and now works in marketing.

He has been complaining of increasing breathlessness, worse on exertion, and is now breathless on climbing a flight of stairs. He has had several faints in the last few months, associated with feeling a 'funny' sensation in his chest, following which he blacks out. On one occasion he sustained a cut on his eye brow. There are no triggers to these episodes and there is a rapid recovery. He has never had any episodes of incontinence or tongue biting.

His past medical history is unremarkable. He was treated with several courses of antibiotics as a child in Brazil for an eye infection that persisted for several months. He has been seeing his GP for the past year for increasingly troublesome constipation. His medications are:

Senna 15mg at night  
Movicol two sachets tds

On examination he has a displaced apex beat, normal heart sounds, and mild coarse crepitations at both lung bases.

What is the likely diagnosis?

[Chagas disease77%](#)[Endomyocardial fibrosis8%](#)[Churg Strauss Syndrome4%](#)[Hypertrophic Obstructive Cardiomyopathy6%](#)[Vasovagal syncope5%](#)

This is Chagas disease caused by *Trypanosoma cruzi*. Keys to the question are presence of Romana's sign (periorbital swelling following inoculation of Trypanosome) as a child, and heart failure and constipation in later life.

## Trypanosomiasis

Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly. *Trypanosoma rhodesiense* tends to follow a more acute course. Clinical features include:

- Trypanosoma chancre - painless subcutaneous nodule at site of infection
- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis

### Management

- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract

- myocarditis may lead to dilated cardiomyopathy (with apical atrophy) and arrhythmias
- gastrointestinal features includes megaesophagus and megacolon causing dysphagia and constipation

### Management

- treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure

### Question 5 of 95

A 28-year-old patient has presented with upper limb weakness. He is extremely anxious and tells you that this morning he noticed that he had a dry mouth and found it difficult to swallow. His friends also commented that his voice sounded different to normal. Several hours later he began to notice weakness in both of his arms. He has not noticed any weakness in his lower limbs. He has no relevant past medical history or family history of note. He smokes 10 cigarettes a day, drinks approximately 30 units of alcohol per week and occasionally injects heroin.

His Glasgow Coma Score is 15/15. Neurological examination reveals power 3/5 in the upper limbs, 5/5 in the lower limbs. Biceps and supinator reflexes are absent. Knee and ankle reflexes are normal. His pupils are dilated and sluggish in reaction to light. He is unable to abduct either eye. You notice needle track marks on the patient's forearm and an erythematous wound in the patient's right antecubital fossa.

What is treatment would you give to the patient immediately?

[IV Beta Interferon6%IV immunoglobulin23%Plasma exchange12%Steroids9%Trivalent antitoxin51%](#)

This patient has presented with typical features of botulism, which is likely to have been contracted via the patient's wound in this case. He has suffered from a descending weakness, initially affecting his bulbar and pharyngeal muscles, then his upper limbs. If untreated this would progress to involve his respiratory muscles and lower limbs. In contrast, Guillain Barré Syndrome (GBS) presents with an ascending weakness usually involving the lower limbs, then upper limbs then cranial nerves. Both conditions show autonomic features and progress rapidly.

One particularly distressing feature of botulism is that it does not affect GCS.

The immediate treatment of choice would be IV Trivalent antitoxin immediately and general supportive measures.

### **Botulism**

*Clostridium botulinum*

- gram positive anaerobic bacillus
- 7 serotypes A-G
- produces botulinum toxin, a neurotoxin which irreversibly blocks the release of acetylcholine
- may result from eating contaminated food (e.g. tinned)
- neurotoxin often affects bulbar muscles and autonomic nervous system

#### Features

- patient usually fully conscious with no sensory disturbance
- flaccid paralysis
- diplopia
- ataxia
- bulbar palsy

Treatment with antitoxin is only effective if given early - once toxin has bound its actions cannot be reversed

#### Therapeutic uses of botulinum toxin

- strabismus
- dystonias: torticollis, blepharospasm
- hyperhidrosis
- cosmetic: Botox: serotype A of botulinum toxin used

#### Question 4 of 95

A 31 year-old male originally from Russia who is known to be HIV positive presents with a rash. On examination there are purple-red cutaneous macules and papules on the back, neck and oral mucosal membrane.

Blood results reveal:

Hb	141 g/l
Platelets	$327 \times 10^9/l$
WBC	$4.2 \times 10^9/l$
Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	3.7 mmol/l
Urea	4.6 mmol/l

Creatinine	59 $\mu\text{mol/l}$
Bilirubin	27 $\mu\text{mol/l}$
ALP	97 u/l
ALT	44 u/l
Albumin	30 g/l
HIV viral load	14,000 copies / ml
CD4 cell count	124 cell/mm <sup>3</sup>

A skin biopsy is performed and the report is below:

Spindle cells present. Mitotic activity is moderate. Abnormally dense and irregular blood vessels. Intracellular hyaline bodies present.

Which virus is likely to be responsible for these lesions?

[CMV10%EBV9%HIV-25%HHV-861%HPV-816%](#)

This is a description of AIDS-related Kaposi's sarcoma.

Kaposi sarcoma is a disease of blood vessels that was considered very rare before the start of the AIDS pandemic. AIDS is due to infection with human immunodeficiency virus (HIV).

There are four types of Kaposi sarcoma:

- The classic type of Kaposi sarcoma affects elderly men of Mediterranean and Middle European descent and in men in Sub-Saharan Africa.
- AIDS-associated Kaposi sarcoma.
- Endemic or African Kaposi sarcoma arises in some parts of Africa in children and young adults.
- Iatrogenic Kaposi sarcoma is due to drug treatment causing immune suppression.

Classic Kaposi sarcoma is rare and unassociated with HIV infection. It most often arises in middle-aged to elderly men of Mediterranean or Jewish descent (less than 10% are women), particularly if they come from a rural environment. They have a higher than expected rate of diabetes mellitus.

AIDS-related Kaposi sarcoma, unlike other forms of the disease, tends to have an aggressive clinical course. It is the most common presentation of Kaposi sarcoma. It has become less common in the US and Europe because of effective HAART treatment for HIV disease.

Kaposi's sarcoma is caused by infection with human herpesvirus 8 (HHV8), also known as Kaposi sarcoma-associated herpesvirus (KSHV) or KS agent

Typical histologic findings include proliferation of spindle cells, prominent slit-like vascular spaces, intracellular hyaline bodies and extravasated red blood cells.

### **HIV: Kaposi's sarcoma**

#### Kaposi's sarcoma

- caused by HHV-8 (human herpes virus 8)
- presents as purple papules or plaques on the skin or mucosa (e.g. gastrointestinal and respiratory tract)
- skin lesions may later ulcerate
- respiratory involvement may cause massive haemoptysis and pleural effusion
- radiotherapy + resection



Kaposi's sarcoma in a patient with HIV

#### Question 1 of 90

A 65 year-old gentleman with type 2 diabetes mellitus and alcoholism presents with fever, headache and neck stiffness. He has a history of previous anaphylactic reaction to penicillin.

On examination the temperature is 37.9°C, respiratory rate is 20 breaths/min and heart rate is 105 beats per minute. Nutritional state and dental hygiene is poor. The chest is clear to auscultation. The abdomen is soft and non-tender. The Glasgow coma scale score is 15, the patient is uncomfortable during pen-torch pupillary examination and neck flexion is limited by pain.

CSF examination reveals:

White Cells 560 per mm<sup>3</sup> (85% polymorphs)

Red cells 8 per mm<sup>3</sup>

Protein 0.9g/L

Glucose 3.3mmol/L (serum glucose 9.2mmol/L)

Gram stain Gram-negative coccobacilli

Which antimicrobial agent should be initiated?

[Vancomycin13%Ceftriaxone30%Chloramphenicol36%Rifampicin9%Gentamicin12%](#)

This patient has meningitis caused by *Haemophilus influenzae*. Immunocompromised patients including those with alcoholism or diabetes are at risk.

Other gram -ve coccobacilli include *Gardnerella vaginalis*, *Chlamydia trachomatis*, *Bordetella pertussis*, *Coxiella burnetti* and *Haemophilus ducreyi* however these would not classically cause meningitis.

Cefotaxime or ceftriaxone would be the first-line treatment for *haemophilus* meningitis however for those with a history of anaphylaxis to penicillin, chloramphenicol is the most appropriate choice.

Chloramphenicol would also be the appropriate choice in meningococcal meningitis in a penicillin-allergic patient.

(Source: BNF)

## **Meningitis: management**

Investigations suggested by NICE

- full blood count
- CRP
- coagulation screen
- blood culture
- whole-blood PCR

- blood glucose
- blood gas

Lumbar puncture if no signs of raised intracranial pressure

## Management

All patients should be transferred to hospital urgently. If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then intramuscular benzylpenicillin may be given, as long as this doesn't delay transit to hospital.

BNF recommendations on antibiotics

Scenario	BNF recommendation
Initial empirical therapy aged < 3 months	Intravenous cefotaxime + amoxicillin
Initial empirical therapy aged 3 months - 50 years	Intravenous cefotaxime*
Initial empirical therapy aged > 50 years	Intravenous cefotaxime + amoxicillin
Meningococcal meningitis	Intravenous benzylpenicillin or cefotaxime
Pneumococcal meningitis	Intravenous cefotaxime
Meningitis caused by <i>Haemophilus influenzae</i>	Intravenous cefotaxime
Meningitis caused by <i>Listeria</i>	Intravenous amoxicillin + gentamicin

If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using chloramphenicol.

Management of contacts

- prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis
- oral ciprofloxacin or rifampicin or may be used. The Health Protection Agency (HPA) guidelines now state that whilst either may be used ciprofloxacin is the drug of choice as it is widely available and only requires one dose
- the risk is highest in the first 7 days but persists for at least 4 weeks
- meningococcal vaccination should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy
- for pneumococcal meningitis no prophylaxis is generally needed. There are however exceptions to this. If a cluster of cases of pneumococcal meningitis occur the HPA have a protocol for offering close contacts antibiotic prophylaxis. Please see the link for more details

\*in the 2015 update of the *NICE Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management* the recommendation for initial empirically therapy for children > than 3 months is intravenous ceftriaxone



Question 2 of 90

An 18-year-old male presents to the general medical take.

He presents with large grey lesions around his perineum and in his mouth which started 2 days ago. He reports that he has a more general rash on his trunk and the palms and soles of his feet. He generally feels unwell with malaise and fever. He has never had anything like this before but mentions that he did see a small ulcer on his scrotum a month ago that didn't hurt and healed on its own.

He reports that he is generally fit and well and has just moved to the area to start his university studies.

On examination, he has a symmetrical, widespread, macular papular rash on his trunk, limbs and the palms and soles of his feet. This is different from the large greyish lesions that you see in his mouth and perineum. He has general lymphadenopathy that is minimally tender on palpation. His chest is clear on auscultation, there are no added heart sounds and his abdomen is soft and non-tender.

Investigations show:

Haemoglobin	13g/dl
WCC	$11 \times 10^9/l$
Platelets	$352 \times 10^9/l$
CRP	89mg/L
Sodium	145 mmol/l
Potassium	3.8 mmol/l
Urea	4 mmol/l
Creatinine	82 $\mu$ mol/l

What is the most likely diagnosis?

[Epstein Barr virus8%HIV9%Cytomegalovirus6%Herpes simplex virus7%Treponema pallidum70%](#)

This young man presents with a symmetrical rash on his trunk, palms, and soles that is pathognomonic for secondary syphilis. He also has a further rash of grey lesions in the mouth and perineum associated with syphilis. Although he was not concerned about it, he has also mentioned that he had a painless genital ulcer one month ago that may have represented his primary syphilis infection. He has general lymphadenopathy and epitrochlear nodes are particularly suggestive of the diagnosis.

He is a young man that has recently started university and is likely to be enjoying this period of parties and new acquaintances. It would be worth exploring his sexual history further as syphilis

is more common in men who have sex with men.

Patients are often co-infected with other sexually transmitted diseases and this patient should be further investigated for these including HIV.

Answers 1,2 and 3 may all be associated with lymphadenopathy, but one would not expect to get genital ulceration or grey mucosal lesions. HIV can be associated with a rash on the limbs, palms and soles.

Answer 4 is associated with genital ulceration, but they are usually multiple, extremely painful and do not cause the systemic symptoms described in this question.

<https://www.bashh.org/documents/UK%20syphilis%20guidelines%202015.pdf>

## **Syphilis**

Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*. Infection is characterised by primary, secondary and tertiary stages. The incubation period is between 9-90 days

### **Primary features**

- chancre - painless ulcer at the site of sexual contact
- local non-tender lymphadenopathy
- often not seen in women (the lesion may be on the cervix)

### **Secondary features - occurs 6-10 weeks after primary infection**

- systemic symptoms: fevers, lymphadenopathy
- rash on trunk, palms and soles
- buccal 'snail track' ulcers (30%)
- condylomata lata



© Image used on license from [DermNet NZ](#)



Classical palm lesions of secondary syphilis



© Image used on license from [DermNet NZ](#)



More generalised rash of secondary syphilis

#### Tertiary features

- gummas (granulomatous lesions of the skin and bones)
- ascending aortic aneurysms
- general paralysis of the insane
- tabes dorsalis

- Argyll-Robertson pupil

#### Features of congenital syphilis

- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- saddle nose
- deafness

#### Question 3 of 90

A 32-year-old gentleman presents to the emergency department with severe nausea, vomiting and diarrhoea. He was recently at a reunion where 18 out of 25 guests have developed similar symptoms shortly afterwards. On examination he appears clinically dehydrated but his vital parameters are all normal. He has no past medical history and otherwise his examination is normal. You suspect norovirus; what is the most appropriate investigation?

[Serum serology7%](#)[Faecal or vomitus toxicology9%](#)[Faecal or vomitus viral PCR60%](#)[Serum toxins7%](#)[Serum viral PCR18%](#)

The correct answer is faecal or vomitus viral PCR which can confirm norovirus infection. Tests can detect antibodies by the ELISA method but these lack sensitivity and specificity and are therefore seldom used in the clinical setting. Norovirus does not make a toxin and therefore there is no such thing as norovirus toxin testing. The virus is not normally present in the bloodstream and therefore serum is likely to be negative for PCR testing. Norovirus is a viral cause of gastroenteritis commonly associated with large outbreaks in winter.

#### Gastroenteritis

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The

most common cause is *Escherichia coli*

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

### Stereotypical histories

Infection	Typical presentation
<i>Escherichia coli</i>	Common amongst travellers Watery stools Abdominal cramps and nausea
Giardiasis	Prolonged, non-bloody diarrhoea
Cholera	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers
<i>Shigella</i>	Bloody diarrhoea Vomiting and abdominal pain
<i>Staphylococcus aureus</i>	Severe vomiting Short incubation period
<i>Campylobacter</i>	A flu-like prodrome is usually followed by crampy abdominal pains, fever and diarrhoea which may be bloody  Complications include Guillain-Barre syndrome Two types of illness are seen
<i>Bacillus cereus</i>	<ul style="list-style-type: none"><li>• vomiting within 6 hours, stereotypically due to rice</li><li>• diarrhoeal illness occurring after 6 hours</li></ul>
Amoebiasis	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks

### Incubation period

- 1-6 hrs: *Staphylococcus aureus*, *Bacillus cereus*\*
- 12-48 hrs: *Salmonella*, *Escherichia coli*
- 48-72 hrs: *Shigella*, *Campylobacter*
- > 7 days: Giardiasis, Amoebiasis

\*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

#### Question 4 of 90

A 23-year-old woman presents to GUM clinic. She reports that two days ago she had unprotected vaginal intercourse with a casual partner, who has informed her that he is HIV positive. He claimed to be taking treatment and having good viral control. He has given her a copy of his most recent letter from his HIV clinic confirming that he is on antiretroviral treatment and that his viral load has been <50 (undetectable) for the last year with a CD4 count of 745 cells/mm<sup>3</sup>. You are able to confirm the validity of this letter as the partner attends the same GUM clinic for his HIV care, and you are also able to confirm the investigations.

She has no past medical history and takes microgynon. She is concerned about catching HIV.

She has undergone STI screening today, including HIV serology. Microscopy is negative for any pathogens. A pregnancy test today is negative.

How should she be further managed?

[Advise repeat STI screen in two weeks and repeat HIV test 8-12 weeks26%](#)[Offer HIV post-exposure prophylaxis38%](#)[Advise repeat HIV test in 8-12 weeks15%](#)[Offer rapid antigen test for HIV and if positive then start HIV post-exposure prophylaxis18%](#)[Offer to refer to HIV clinic3%](#)

The correct answer is to advise repeat STI screen in two weeks and repeat HIV test 8-12 weeks. She has had a low risk of exposure to HIV. As her sexual partner has a sustained undetectable viral load for over six months and is confirmed to be on antiretroviral treatment she is at low risk of contracting HIV and therefore does not need post-exposure prophylaxis or rapid antigen testing. The most appropriate option is, therefore, to offer a repeat STI screen in two weeks and repeat HIV test in 8-12 weeks. There is no point in referring to HIV clinic at this point as she does not have any positive results.

Source:

Cresswell, F., L. Waters, E. Briggs, J. Fox, J. Harbottle, D. Hawkins, M. Murchie, K. Radcliffe, P. Rafferty, A. Rodger, and M. Fisher. 'UK Guideline for the Use of HIV Post-Exposure Prophylaxis Following Sexual Exposure, 2015.' International Journal of STD & AIDS 27.9 (2016): 713-38.

### **Post-exposure prophylaxis**

Hepatitis A

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation

## Hepatitis B

- HBsAg positive source: if the person exposed is a known responder to HBV vaccine then a booster dose should be given. If they are in the process of being vaccinated or are a non-responder they need to have hepatitis B immune globulin (HBIG) and the vaccine
- unknown source: for known responders the green book advises considering a booster dose of HBV vaccine. For known non-responders HBIG + vaccine should be given whilst those in the process of being vaccinated should have an accelerated course of HBV vaccine

## Hepatitis C

- monthly PCR - if seroconversion then interferon +/- ribavirin

## HIV

- a combination of oral antiretrovirals (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) as soon as possible (i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- serological testing at 12 weeks following completion of post-exposure prophylaxis
- reduces risk of transmission by 80%

## Varicella zoster

- VZIG for IgG negative pregnant women/immunosuppressed

## Estimates of transmission risk for single needlestick injury

**Hepatitis B 20-30%**

Hepatitis C 0.5-2%

HIV 0.3%

#### Question 5 of 90

A 28-year-old woman who is 13-weeks pregnant is referred into the medical admissions unit by the general practitioner. Her 2-year-old son has developed a blistering generalised rash, which you suspect may be chicken pox. She feels well with no respiratory symptoms and has no evidence of rash. On questioning she does not remember contracting chickenpox as a child. What is the next appropriate step?

[Discharge and reassure4%](#) [Administer varicella-zoster immunoglobulin \(VZIG\)31%](#) [Vaccinate against varicella6%](#) [Check varicella zoster virus IgG53%](#) [Oral aciclovir prophylaxis6%](#)

The first step is to assess whether she is immune to varicella by checking her varicella zoster serology. If she is immune (varicella zoster virus IgG positive) then there is no risk to the foetus - even if she were to develop shingles.

The Royal College of Obstetrics and Gynaecology (RCOG) guidelines state:

If the pregnant woman is not immune (varicella zoster virus IgG negative) and she has had a significant exposure, she should be offered varicella-zoster immunoglobulin (VZIG) as soon as possible. VZIG is effective when given up to 10 days after contact. Non-immune pregnant women who have been exposed to chickenpox should be managed as potentially infectious from 28 days after exposure if they receive VZIG and from 21 days after exposure if they do not receive VZIG.

(<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg13/>)

The varicella vaccine contains a live attenuated virus and so is contraindicated in pregnant women and immunosuppressed patients. Postpartum varicella immunisation should be discussed.

Oral acyclovir prophylaxis is not recommended.

### **Chickenpox exposure in pregnancy**

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion. In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Risks to the mother

- 5 times greater risk of pneumonitis



### Fetal varicella syndrome (FVS)

- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

### Other risks to the fetus

- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester
- severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

### Management of chickenpox exposure

- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently checked for varicella antibodies
- if the pregnant woman is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure
- consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

### Question 6 of 90

A 40-year-old male presented to the Emergency Department with a decreasing level of consciousness. He had just returned from the Hajj pilgrimage in Saudi Arabia. He was completely healthy during his travels, but he started to develop a fever 2 days after his return. The fever was associated with a severe frontal headache and photophobia. These symptoms persisted for the last two days and he started to become sleepier.

On examination: blood pressure 100/80 mmHg, pulse rate 120/min, temperature 39.2°C, respiratory rate 27/min. He had evidence of neck stiffness. Blood investigations showed:

Hb 123 g/l

Platelets  $130 \times 10^9/l$

WBC  $13 \times 10^9/l$

What is the most likely diagnosis?

[Meingiococcal meningits type A35%Meingiococcal meningits type B21%Meingiococcal meningits type C30%Malaria7%Hemorrhagic fever8%](#)

The candidate should have no difficulty in recognising that this patient has meningitis. However, good knowledge of the epidemiology of meningitis is required to answer the question completely.

The most common cause of meningitis in Saudi Arabia during Hajj is meningococcal meningitis type A. It is also the main cause of epidemics of what is known as the meningitis belt in Africa along the equator line including Sudan, Ethiopia and Nigeria.

Type B and Type C are mainly responsible for sporadic cases of meningitis in Europe and South America.

Source <http://www.who.int/csr/resources/publications/meningitis/whoemcbac983.pdf>

## **Meningitis: causes**

0 - 3 months

- Group B *Streptococcus* (most common cause in neonates)
- *E. coli*
- *Listeria monocytogenes*

3 months - 6 years

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

6 years - 60 years

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

> 60 years

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Listeria monocytogenes*

Immunosuppressed

- *Listeria monocytogenes*

Question 7 of 90

A returning traveller presents to the emergency department with a 10 day history of fever, cough and abdominal pain. He has spent the last 2 weeks in Jakarta, Indonesia. His vital signs are: temperature: 40.1°C, heart rate 85 beats/minute, blood pressure 120/80 mmHg

On examination his spleen is enlarged and there is a rose spot rash over the chest. Blood culture grows salmonella typhi and the on-call doctor diagnoses enteric fever (typhoid).

If left untreated, what is the most important and serious complication that can occur within the following 2 weeks?

[Chronic carriage within gallbladder8%Bowel perforation and haemorrhage 54% Splenic infarction and rupture21% Acute liver failure8%Bacterial meningitis9%](#)

The most serious and frequent complications of Typhoid are bowel perforation and haemorrhage. This is caused by bacterial destruction of the Peyer's patches in the small intestine and classically occurs late in the second week of illness or early in the third week. Other complications include myocarditis and endocarditis.

Chronic bacterial carriage in the gall bladder does occur, but this is not the most serious complication. It renders the patient chronically infective and capable of transmitting the disease. Acute liver failure does not occur, but mild jaundice may result from cholecystitis or hepatitis. Bacterial meningitis is a very rare complication not often reported.

***Salmonella***

The *Salmonella* group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi* (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, arthralgia

#### Features

- initially systemic upset as above
- relative bradycardia
- abdominal pain, distension
- constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid
- rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

#### Possible complications include

- osteomyelitis (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%, more likely if adult females)

#### Question 8 of 90

A 23 year-old artist presents after he woke up with headache, neck stiffness, and photophobia. He is normally fit and well, but for the last three weeks has complained of feeling tired and irritable.

On examination, the left side of the palate does not elevate, and the tongue is deviated to the left upon protrusion. The remainder of the neurological examination is unremarkable.

Plain computed tomography of the head is unremarkable.

Lumbar puncture is performed with results of CSF analysis as follows:

Appearance	Turbid
------------	--------

White blood cells	28 cells/mm <sup>3</sup> (95% lymphocytes)
Red blood cells	<1 cells/mm <sup>3</sup>
Gram stain	No organisms seen
Protein	1.32 g/L
Glucose	1.4 mmol/L
Serum glucose	7.5 mmol/L

What is the most likely diagnosis?

[Meningococcal meningitis 11%](#) [Tuberculous meningitis 69%](#) [Subarachnoid haemorrhage 5%](#) [Skull base tumour 6%](#) [Malignant meningitis 10%](#)

The prodromal phase of malaise and possible personality change, followed by meningism, with the onset of basal cranial nerve palsies, and coupled with the CSF findings of lymphocytic pleocytosis, raised protein, and low glucose, are all highly suggestive of tuberculous meningitis.

There is no particular suggestion of a primary malignancy, but malignant meningitis (leptomeningeal carcinomatosis) is a possibility and it would be reasonable to send a large volume of CSF for cytology. Like tuberculous meningitis, this condition typically presents with headache, meningism, and cranial nerve palsies. However, it is eye movements which are most often affected. There is often also invasion of spinal meninges which involves nerve roots and mimics radiculopathy. The CSF is hardly ever normal, although there are no specific features other than the direct demonstration of malignant cells.

Meningococcal meningitis is an acute disease, so the three week prodrome described here would be unusual. The presence of cranial nerve palsies would be extremely unusual. The CSF would be expected to show a neutrophilic pleocytosis, with a low glucose (less than 50% of serum glucose), but not as low as in tuberculous meningitis.

Subarachnoid haemorrhage should be considered in any case of acute headache. The normal CT scan is reassuring but does not exclude the diagnosis, but in any case the CSF is not suggestive.

A tumour of the skull base might explain the lower cranial nerve palsies, but one would have expected some more suggestive symptoms and an abnormal CT head. This diagnosis would not explain the grossly abnormal CSF findings.

## **Meningitis: CSF analysis**

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in meningitis:

	Bacterial	Viral	Tuberculous
<b>Appearance</b>	Cloudy	Clear/cloudy	Slight cloudy, fibrin web
<b>Glucose</b>	Low (< 1/2 plasma)	60-80% of plasma glucose*	Low (< 1/2 plasma)
<b>Protein</b>	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
<b>White cells</b>	10 - 5,000 polymorphs/mm <sup>3</sup>	15 - 1,000 lymphocytes/mm <sup>3</sup>	10 - 1,000 lymphocytes/mm <sup>3</sup>

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)

\*mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

#### Question 9 of 90

A 15-year-old male is investigated following a one week history of fever, non-productive cough, sore throat and headaches. Today he noticed a skin rash. His temperature is 38.5°C, pulse is 90/min, blood pressure is 115/78 mmHg and respirations are 16/min.

On examination his throat is hyperaemic, but there is no cervical lymphadenopathy. Chest auscultation and percussion reveal no abnormalities. You note dusky red, target shaped skin lesions over all four extremities. Chest x-ray reveals interstitial infiltrates in the left lower lobe. Sputum Gram stain reveals polymorphonuclear cells but no organisms.

Which of the following organisms is most likely responsible for this presentation?

[\*Streptococcus pneumoniae\*10%](#)[\*Haemophilus influenzae\*7%](#)[\*Legionella pneumophila\*5%](#)[\*Mycoplasma pneumoniae\*65%](#)[Epstein Barr virus13%](#)

This young man presents with a history suggestive of atypical pneumonia. Atypical pneumonia is distinguished from typical pneumonia by its more indolent course, non-productive cough and higher incidence of extra-pulmonary symptoms. This patient's low grade fever and weeks worth of symptoms are consistent with an indolent course. Furthermore, he has multiple extra-pulmonary symptoms including headache, sore throat and skin rash. The different types of atypical pneumonia can present similarly and are at times challenging to distinguish. In this case, the skin rash (erythema multiforme) is typical of *Mycoplasma*. *Mycoplasma* is an organism that does not have a cell wall, and therefore does not stain with Gram stain; hence the finding of only polymorphonuclear cells on sputum Gram stain analysis.

Choice 1: *Pneumococcus* is the most frequent cause of community-acquired pneumonia

requiring hospitalisation. Cough is often productive of rusty-coloured sputum. Compared to atypical pneumonias, pneumococcal pneumonia causes fewer extra-pulmonary manifestations but has a more virulent course. Sputum Gram stain would reveal Gram positive diplococci.

Choice 2: *Haemophilus influenzae* is another common cause of community-acquired pneumonia. It presents like a typical pneumonia. Sputum Gram stain reveals small Gram negative bacilli.

Choice 3: *Legionella pneumophila* causes pneumonia with extra-pulmonary symptoms. Environmental water sources are often involved in its spread. It occurs most frequently in elderly patients and smokers. The urine *Legionella antigen* test is helpful in making the diagnosis.

Choice 5: Epstein Barr virus causes infectious mononucleosis, common in adolescents. Sore throat is the most common presenting symptom. Fatigue, malaise, headache and abdominal pain are also common. Concomitant pneumonia is not usually seen.

### ***Mycoplasma pneumoniae***

*Mycoplasma pneumoniae* is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

#### Features

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

#### Complications

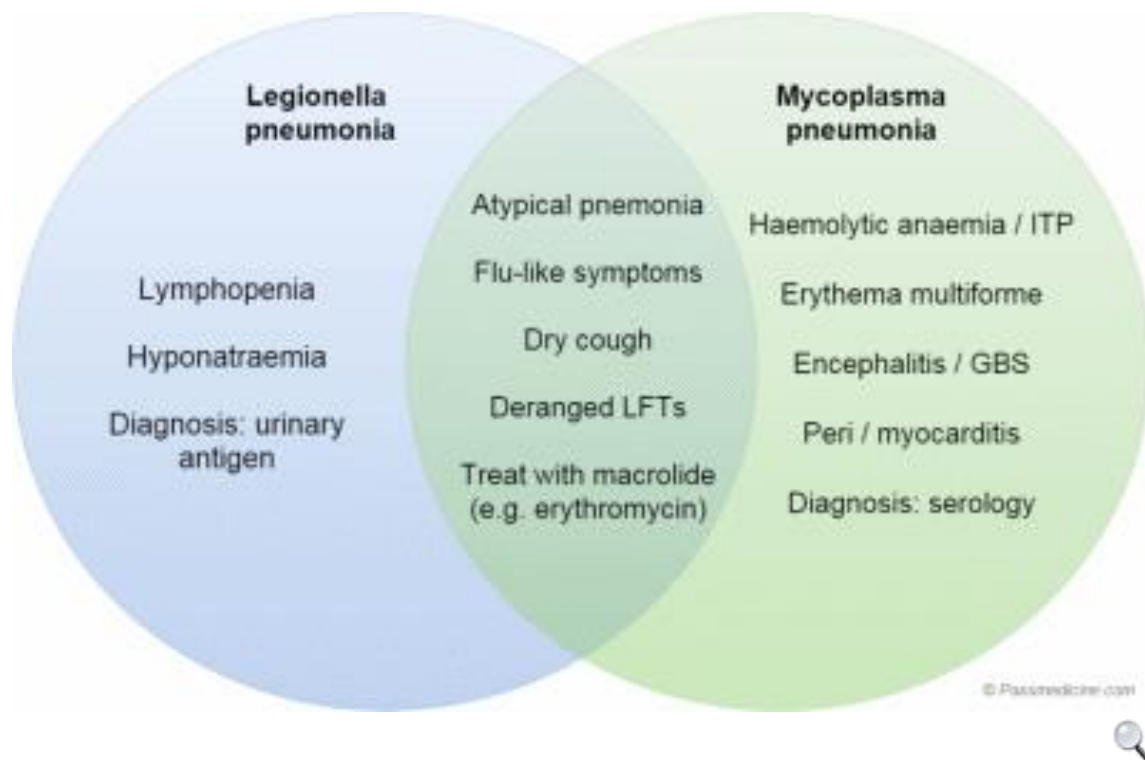
- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

## Investigations

- diagnosis is generally by Mycoplasma serology
- positive cold agglutination test

## Management

- erythromycin/clarithromycin
- tetracyclines such as doxycycline are an alternative



## Comparison of Legionella and Mycoplasma pneumonia

### Question 10 of 90

A 27-year-old man who recently immigrated to the UK from Ethiopia complains of a chronic cough with night sweats for five weeks. On direct questioning, he also admits coughing up small volumes of bright red blood a few times. This has made him especially concerned as he his father died from lung related problems following chronic coughs.

Following a chest X-ray and blood tests he is diagnosed with TB and contact tracing is started. His 25-year-old male partner lives with him and is identified as being at high risk of contracting



TB. The partner undergoes Mantoux testing and has a 2mm area of induration. He has never had BCG vaccination as far as he is aware and has no vaccination scar. What is the most appropriate management that should be offered to the partner?

[BCG vaccination14% HIV testing and if negative then BCG vaccination40% Prophylactic anti-TB treatment28% Repeat TB screening in six weeks10% No further management needed8%](#)

The correct answer is HIV testing and if negative then BCG vaccination. The low area of response to the Mantoux testing indicates that he is unlikely to have TB and has not been vaccinated. However, the test can be a false negative result in an immunosuppressed patient. As the partner is at increased risk of HIV, NICE advises that an HIV test should be done prior to vaccination. BCG vaccination is a live vaccination and therefore is contraindicated in an immunosuppressed patient. Of note, previous vaccination can lead to a false positive result.

NICE advises that once a diagnosis of pulmonary TB has been made then close contacts should be managed as follow:

- If asymptomatic and younger than 65 years then test for latent TB. If Mantoux-negative and unvaccinated then offer vaccination. If at risk of HIV then test for HIV first.
- If asymptomatic and older than 65 years then assess with a chest X-ray.

Treatment for TB should be considered if TB is confirmed and not used prophylactically. Repeat screening is generally not used.

Source:

'Tuberculosis NICE Guidelines.' The National Institute for Health and Care Excellence, 13 Jan. 2016.

## **Tuberculosis: screening**

The Mantoux test is the main technique used to screen for latent tuberculosis. In recent years the interferon-gamma blood test has also been introduced. It is used in a number of specific situations such as:

- the Mantoux test is positive or equivocal
- people where a tuberculin test may be falsely negative (see below)

## **Mantoux test**

- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected intradermally
- result read 2-3 days later

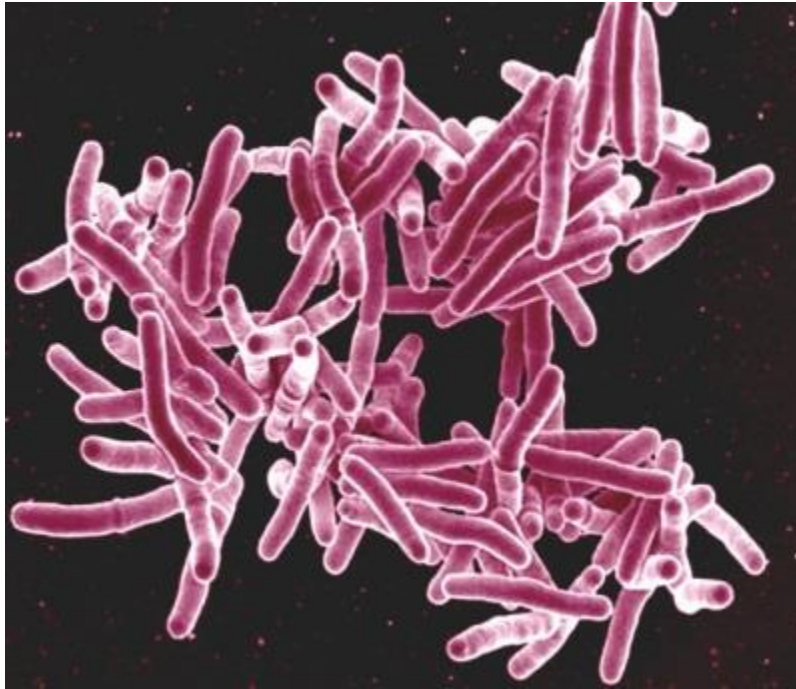
<b>Diameter of induration</b>	<b>Positivity</b>	<b>Interpretation</b>
< 6mm	Negative - no significant hypersensitivity to tuberculin protein	Previously unvaccinated individuals may be given the BCG
6 - 15mm	Positive - hypersensitive to tuberculin protein	Should not be given BCG. May be due to previous TB infection or BCG
> 15mm	Strongly positive - strongly hypersensitive to tuberculin protein	Suggests tuberculosis infection.

False negative tests may be caused by:

- miliary TB
- sarcoidosis
- HIV
- lymphoma
- very young age (e.g. < 6 months)

### **Heaf test**

The Heaf test was previously used in the UK but has been since been discontinued. It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.



Scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, which cause TB. Credit: NIAID

#### Question 1 of 89

A 48-year-old man attends the clinic for review. He complains of tiredness and weakness. He has a past medical history of alcoholism and currently drinks 88 units of beer per week. He takes regular thiamine. He is euvolaemic on examination.

Blood results are as follows:

Hb	122 g/l	Na <sup>+</sup>	128 mmol/l
Platelets	$385 \times 10^9/l$	K <sup>+</sup>	3.6 mmol/l
WBC	$8.5 \times 10^9/l$	Urea	3.2 mmol/l
Neuts	$4.6 \times 10^9/l$	Creatinine	38 $\mu\text{mol/l}$
Lymphs	$2.2 \times 10^9/l$	CRP	8 mg/l

A paired serum and urine test is as follows:

Serum osmolality 271mOsm/kg (normal range 285-295)

Urine osmolarity 50 mOsm/kg (low)

Urinary sodium 8 mmol/l (low)

What is the most likely diagnosis?

[Hypothyroidism9%Potomania50%SIADH20%Addison's disease6%Diabetes insipidus15%](#)

Beer potomania is a cause of hyponatremia which occurs due to a low dietary intake of solutes. Urine osmolarity will be low (<100 mosmol/kg) indicating that ADH is appropriately suppressed. Identifying the cause of hyponatraemia can be challenging. The first step is to confirm that it is a true hypotonic hyponatraemia. This is done by measuring the plasma osmolarity.

- If the measured plasma osmolarity is low this confirms true hypotonic hyponatraemia.
- If the plasma osmolarity is normal then this is suggestive of pseudohyponatraemia and should prompt you to measure proteins and lipids, which if present in high levels, can cause a pseudohyponatraemia due to the measuring technique.
- If the serum osmolarity is high then this confirms hypertonic hyponatraemia and should prompt you to check for high levels of solutes in the plasma, hyperglycaemia being the most common.

To identify the cause of the hyponatraemia there are several crucial considerations

- Volume status of the patient: hypervolaemic, euvolaemic, or hypovolaemic
- Paired serum and urine osmolarities
- Urinary sodium
- Thyroid and adrenal function
- History of patient e.g. diarrhoea, burns, vomiting, and kidney dysfunction. This is extremely important as may give clues to the cause (e.g. we could expect hypovolaemia and hyponatraemia with prolonged diarrhoea due to excessive loss of fluid and sodium from the GI tract)
- Drug history: several drugs are implicated in hyponatraemia through several mechanisms including SIADH

In this case, the low measured serum osmolarity confirms a true hypotonic hyponatraemia. The decreased plasma sodium can occur due to too much fluid (e.g. decreased urinary output or increased oral intake) or too little sodium (e.g. decreased oral intake or increased output through kidneys, GI tract, or skin). It can also be due to a combination of disturbed water and sodium balance e.g. combined sodium and water loss with a greater amount of sodium loss.

In this case, the patient is euvolaemic which narrows down the differential. Euvolaemic hyponatraemia can occur due to:

- Hypothyroidism
- Psychogenic polydipsia

- Beer potomania

It is now very important to consider the urine osmolarity and sodium.

Urinary sodium is arguably the most useful biochemical measurement. Some key points include:

- In hyponatremia we would expect a low urinary sodium as the body attempts to conserve sodium
- Therefore a high urinary sodium  $>20$  in the presence of hyponatraemia suggests renal sodium loss (e.g. CKD, diuretics, and salt losing nephropathy). Other causes of high urinary sodium include endocrine disease (e.g. Addison's), primary polydipsia, SIADH and reset osmostat
- A low urinary sodium ( $<20$ ) in the presence of hyponatraemia suggest that the kidneys are conserving sodium. This should prompt you to consider extra-renal sodium losses (e.g. via GI tract or skin).
- Urinary sodium must be interpreted with caution. For example, if a patient is on diuretics the urinary sodium may be high after taking them but may go very low after their effects wear off, particularly if the patient is dehydrated
- The RAAS system is the dominant factor in sodium balance so consider this carefully
- In secondary hyperaldosteronism (e.g. heart failure, and cirrhosis) we get increased sodium retention and therefore a low urinary sodium
- In hypoaldosteronism (e.g. Addison's, true hypervolaemic states (e.g. polydipsia, SIADH)) we get high urinary sodium

Some key points with regards to urine osmolarity:

- In the presence of hyponatremia the bodies natural response to raising sodium would be to increase free water output resulting in a high urinary output with low urine osmolarity
- Urine osmolarity helps to differentiate between conditions associated with impaired free water excretion (high urine osmolarity  $>100$ ), as seen in the majority of cases, and a few conditions associated with low urine osmolarity  $<100$
- Urine osmolarity  $< 100$  suggests that the kidneys are not concentrating urine e.g. ADH is suppressed
- Urine osmolarity  $> 100$  suggests that ADH is not suppressed and is concentrating urine and impairing free water excretion
- Urine osmolarity will be raised in the majority of cases of hyponatraemia either due to inappropriate ADH release (e.g. SIADH), appropriate ADH release (hypovolaemia) or pseudo “appropriate” ADH release (perceived intravascular depletion but actual hypervolaemic states e.g. heart failure and cirrhosis)
- With primary polydipsia, malnutrition (e.g. tea and toast syndrome, beer potomania) and a reset osmostat, the urine osmolarity is maximally dilute and generally less than 100

In this example, the history of excessive beer consumption, euvolaemic fluid status, low urine

osmolarity, and a low urinary sodium, makes beer drinkers potomania the most likely cause of the hyponatraemia.

Potomania, also known as beer drinker's potomania is a specific hypo-osmolality syndrome related to massive consumption of beer, which is poor in solutes and electrolytes. With little food or other sources of electrolytes, consumption of large amounts of beer or other dilute alcoholic drinks leads a low level of urinary solute excretion (approximately 200-300 mOSM). This limits the amount of free water excretion to approximately 4 litres. Any intake above 4 litres would lead to a dilution of the serum sodium concentration and thus hyponatraemia.

## **Hyponatraemia**

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis

### **Urinary sodium > 20 mmol/l**

Sodium depletion, renal loss (patient often hypovolaemic)

- diuretics
- Addison's
- diuretic stage of renal failure

Patient often euvolaemic

- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

### **Urinary sodium < 20 mmol/l**

Sodium depletion, extra-renal loss

- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)

- secondary hyperaldosteronism: heart failure, cirrhosis
- reduced GFR: renal failure
- IV dextrose, psychogenic polydipsia

#### Question 1 of 80

A 44-year-old man presents with a 1 day history of fever. He returned to the UK 12 days ago after visiting his family in northern Uganda. He has been resident in the UK for the last 20 years and returns home on average once a year. He does not routinely take malaria prophylaxis.

On examination his temperature is 39.4°C, pulse is 86 beats per minute, his blood pressure is 115/78 mmHg and his oxygen saturations are 98% on air. The remainder of the physical examination is normal. A thick and thin blood film are sent to the lab which confirms *Plasmodium falciparum* malaria. The report reads 2.1% parasitaemia with the presence of schizonts.

What is the most appropriate initial management strategy?

[Intravenous artesunate 68%](#) [Oral quinine sulfate 5%](#) [Oral chloroquine 7%](#) [Oral atovaquone-proguanil \(Malarone\) 12%](#) [Intravenous quinine 8%](#)

This question examines your ability to differentiate severe malaria from uncomplicated malaria and then apply the correct therapy.

We are told the patient has been living in the UK for the last 20 years. As a result any natural immunity built up in earlier life would have dramatically reduced putting him at high risk of developing severe malaria with a relatively low level parasitaemia.

The most important information given is that schizonts are present in the blood film. Schizonts are the final step before red blood cells rupture and release more parasites (merozoites) into the blood.

Given his lack of immunity and an impending rise in parasitaemia it would be pertinent to consider this a case of severe malaria and treat accordingly with intravenous therapy early on. This excludes answers B, C and D. Furthermore chloroquine is only used routinely in the treatment of non falciparum malaria.

WHO guidelines recommend the use of intravenous artesunate for at least the first 24 hours until the patient can tolerate oral medication.

## **Malaria: Falciparum**

### Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 °C
- severe anaemia
- complications as below

### Complications

- cerebral malaria: seizures, coma
- acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
- acute respiratory distress syndrome (ARDS)
- hypoglycaemia
- disseminated intravascular coagulation (DIC)

### Uncomplicated falciparum malaria

- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

### Severe falciparum malaria

- a parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse



### Question 2 of 80

A 23-year-old gentleman presents to GUM clinic. He has been referred by his GP as he presented with dysuria and a negative urine dipstick test. A sexual health screen, including blood tests for HIV and syphilis serology, are requested. What form of consent is required?

[No consent9%](#)[Implied consent8%](#)[Verbal consent53%](#)[Written consent9%](#)[Written consent for HIV testing and verbal consent for sexual health screening22%](#)

The correct answer is verbal consent. Consent clearly is needed as an investigation is done but since syphilis and HIV are transmittable diseases consent needs to be specific towards each. This means that the patient must be aware that they are being tested for HIV and syphilis rather than just aware that they are having a routine blood test. Written consent is not needed, and may discourage patients from having testing.

Source:

UK National Guidelines for HIV Testing 2008. London: British HIV Association, 2008 (see page 10)

### **HIV: seroconversion**

HIV seroconversion is symptomatic in 60-80% of patients and typically presents as a glandular fever type illness. Increased symptomatic severity is associated with poorer long term prognosis. It typically occurs 3-12 weeks after infection

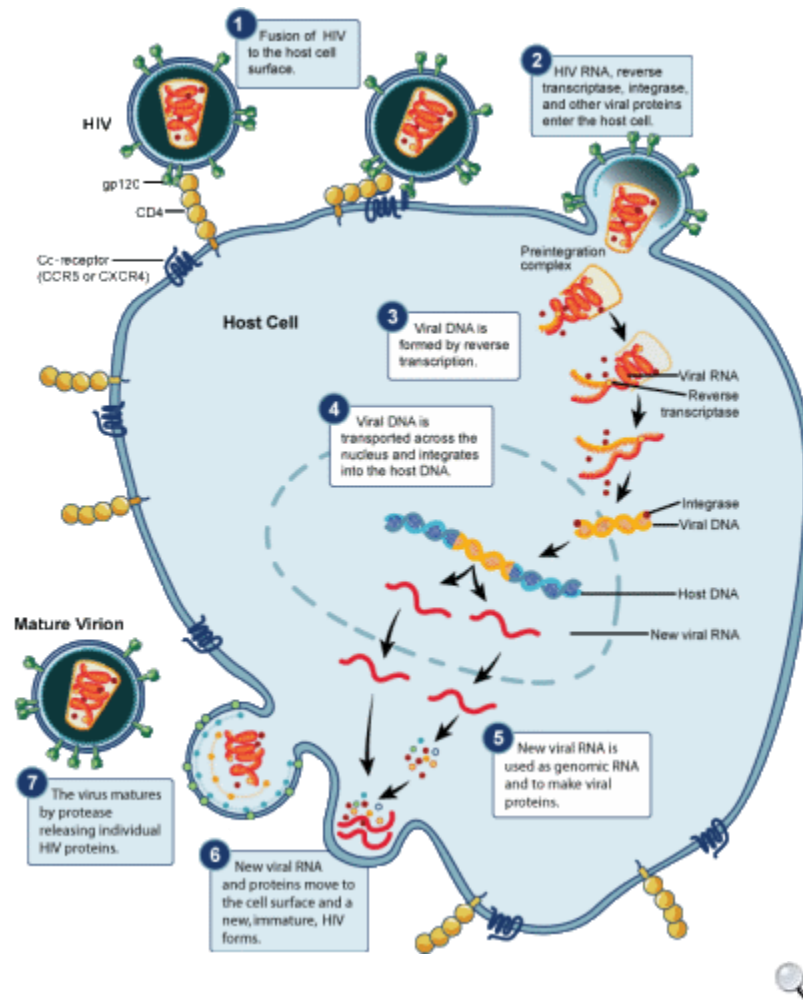
#### Features

- sore throat
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea
- maculopapular rash
- mouth ulcers
- rarely meningoencephalitis

#### Diagnosis

- antibodies to HIV may not be present

- HIV PCR and p24 antigen tests can confirm diagnosis



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

### Question 3 of 80

A 30-year-old man is repatriated to the UK from China after being savaged by a dog. He had been working in rural China as an engineer with a non-government organisation. Ten days previously he had been attacked by dog in the street and bitten repeatedly on the right arm. The dog was reported as having been acting very aggressively. It had subsequently been caught and euthanised.

The patient had received prompt local medical attention. His wounds had been washed out in theatre and a course of intravenous antibiotics commenced. Due to issues with tissue loss and possible tendon damage he had been repatriated to the UK for plastic surgery.

As part of the above treatment, the patient had received a full dose of rabies immunoglobulin infiltrated into his wounds two days after the assault. Medical records sent with the patient stated that a course of rabies vaccination had also been initiated, with three doses given so far at day 1, day 4 and day 8 after the injury. The vaccination schedule to date is consistent with the 5 dose Essen regime recommended by the WHO. To complete this schedule, two further doses of vaccination should be given at 14 and 28 days after the first dose.

The recorded serial number of the vaccinations given was checked and found to represent a form of nerve tissue vaccination. On review of current UK supplies this was not found to be available, with only cell culture and embryonate egg-based vaccinations (CCEEVs) in stock. It was also confirmed with the patient that he had never received a course of rabies vaccination previously.

What is the correct ongoing management of this patients rabies post-exposure prophylaxis?

[Complete vaccination schedule with imported nerve tissue vaccine9% Additional dose rabies immunoglobulin and complete vaccination schedule using available CCEEVs15% Additional dose rabies immunoglobulin and restart vaccination schedule using available CCEEV25% Restart vaccination schedule using available CCEEVs34% Complete vaccination schedule using available CCEEVs18%](#)

The patient has had a high-risk exposure for rabies and requires comprehensive post-exposure prophylaxis. Modern CCEEVs are effective than older nerve tissue vaccination and have a lower incidence of side effects. Therefore, it is recommended to restart the vaccination course with CCEEVs when initial treatment has been given with nerve tissue vaccine.

The patient has already been appropriately treated with rabies immunoglobulin and a further dose is not required. Immunoglobulin provides passive antibodies at the site of exposure and are of benefit if given within seven days of the initial vaccination dose prior to the development of an active immune response.

Crowcroft N, Thampi N. The prevention and management of rabies. BMJ 2015;350:g7827.

## **Rabies**

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus (specifically a lyssavirus) and has a bullet-shaped capsid. The vast majority of cases are caused by dog bites but it may also be transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Rabies is estimated to still kill around 25,000-50,000 people across the world each year. The vast

majority of the disease burden falls on people in poor rural areas of Africa and Asia. Children are particularly at risk.

#### Features

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at-risk countries:

- the wound should be washed
- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination. If possible, the dose should be administered locally around the wound

If untreated the disease is nearly always fatal.

#### Question 1 of 77

A 34-year-old lady presents to the emergency department.

She moved to the UK from India 10 years ago but moved to the area 3 years ago. She works as a medical coder in the hospital.

She presents with a 3-day history of severe generalised headache, a stiff and painful neck, photophobia, and fever. Her husband reports she is drowsy and has been confused since that morning.

She is generally well and takes no medications. Her only previous medical history is of groin lymphadenopathy that was investigated 5 years ago. A biopsy was taken which showed a caseating granuloma. She had no further follow-up at that time.

Investigations:

Chest x-ray lung fields clear. No obvious abnormalities

Blood tests:

Haemoglobin 138 g/L

White cells	20.3x10 <sup>9</sup> /L
Platelets	310x10 <sup>9</sup> /L
CRP	>350mg/L
Glucose	6.8 mmol/L

Cerebrospinal Fluid (CSF): Appears turbid

Opening pressure	20 cmCSF
Protein	3280 mg/dL
White cells	466 cell/ $\mu$ L (polymorphonucleocytes 280 cell/ $\mu$ L and lymphocytes 206 cell/ $\mu$ L)
Red cells	4 cell/ $\mu$ L
Glucose	1.6 mmol/L
Lactate	5.6 mmol/L
CSF gram stain and PCR	pending

What is the best therapeutic regimen for this patient?

[Start empirical ceftriaxone, vancomycin and dexamethasone14% Await gram stain and viral PCR prior to starting a targeted therapy4% Start aciclovir, ceftriaxone and vancomycin7% Start isoniazid, rifampicin, pyrazinamide and ethambutol22% Start isoniazid, rifampicin, pyrazinamide and ethambutol as well as ceftriaxone, vancomycin and dexamethasone54%](#)

This lady could have either bacterial meningitis or tuberculosis (TB) meningitis from her CSF results.

Although she has no chest signs of previous TB, she has had a previous biopsy suggesting she may have TB in her lymphatic system. This makes TB meningitis the most likely diagnosis, however, treatment should certainly be started empirically. This rules out answer 2 as the correct one. Since the gram stains and stain for acid fast bacilli would not yet be back from the lab, treatment should be started for both bacterial and TB meningitis.

Answers 1 and 3 do not include TB therapy and answer 4 does not cover for bacterial meningitis, therefore, these are incorrect answers.

<https://www.britishinfection.org/files/3014/1617/4211/CNSTB2009Thwaites.pdf>

## Tuberculosis: management

Stop medication if LFT's > 5 times normal limit

Immune reconstitution disease

- occurs typically 3-6 weeks after starting treatment
- often presents with enlarging lymph nodes

### Question 2 of 77

An 80-year-old lady presents from a nursing home with a one-day history of fevers, drowsiness and vomiting. She has been unwell, not eating for the past 3 days according to her carer. Recently she has been exhibiting behavioural changes, crying and agitation when lights are turned on in the room, and holding her neck. She has a background of Alzheimer's dementia, hypertension, congestive cardiac failure (CCF) and chronic kidney disease.

On examination, she is febrile with a temperature of 38.1°C. Heart rate 112 bpm, respiratory rate 20 breaths per minute and oxygen saturations of 94% on air. On auscultation, there are bibasal crepitations and cardiovascular examination is consistent with mild CCF. There is neck stiffness and photophobia on cranial nerve examination, pupils equal and reactive to light. Kernig's sign is positive.

Investigations:

Na <sup>+</sup>	129 mmol/l
K <sup>+</sup>	4.8 mmol/l
Urea	10.9 mmol/l
Creatinine	123 µmol/l
Serum glucose	5.9 mmol/l
C Reactive protein	95 mg/l
Haemoglobin	126 g/l
White cell count	16.4 × 10 <sup>9</sup> /L
INR	1.2

Cerebro-spinal fluid (CSF) analysis:

Opening pressure 25 cmH<sub>2</sub>O

Protein 1.8 g/L

Glucose 2.6 mmol/l

White cell count >1000 per mm<sup>3</sup>  
Gram Stain Gram-positive rods seen  
Colour Cloudy, turbid

What is the likely causative organism?

[Streptococcus pneumoniae 11% Listeria monocytogenes 64% Staphylococcus aureus 6% Neisseria meningitidis 11% Haemophilus influenzae 8%](#)

This lady has bacterial meningitis as evidenced from her LP results. There is only one gram-positive bacilli in the list and that is *Listeria monocytogenes*, a common causative organism of meningitis in the extremes of age.

Gram-positive bacilli (or rods): ABCDL

- Actinomyces
- Bacillus anthracis
- Clostridium, Corynebacterium
- Diphtheria
- Listeria monocytogenes

Gram positive cocci:

- Streptococci
- Staphylococci

Gram-negative cocci: NNM

- Neisseria (Neisseria meningitides, Neisseria gonorrhoea)
- Moraxella

Gram negative bacilli (or rods): almost every other pathogenic gram negative bacteria.

- Salmonella spp.
- Escherichia spp.
- Pseudomonas
- Bacteroides

## Listeria

*Listeria monocytogenes* is a Gram positive bacillus which has the unusual ability to multiply at low temperatures. It is typically spread via contaminated food, typically unpasteurised dairy products. Infection is particularly dangerous to the unborn child where it can lead to miscarriage.

Features - can present in a variety of ways

- diarrhoea, flu-like illness
- pneumonia , meningoencephalitis
- ataxia and seizures

Suspected Listeria infection should be investigated by taking blood cultures. CSF may reveal a pleocytosis, with 'tumbling motility' on wet mounts

Management

- Listeria is sensitive to amoxicillin/ampicillin (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

In pregnant women

- pregnant women are almost 20 times more likely to develop listeriosis compared with the rest of the population due to changes in the immune system
- fetal/neonatal infection can occur both transplacentally and vertically during child birth
- complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- treatment is with amoxicillin

Question 3 of 77

A 26-year-old woman presents to the Emergency Department with a one week history of cough, fever and headache. She returned from Indonesia one week ago.

On examination she appears drowsy and a little muddled. She has no photophobia or focal neurological deficit. She has mild hepatosplenomegaly but no palpable lymphadenopathy. Her chest is clear and heart sounds are normal. She has a macular rash on both legs with a greyish-black scab-like lesion on her left shin.

Investigations results:



Chest x-ray: Bilateral patchy consolidation

Blood culture: Pending

Hb 120 g/l

Platelets  $130 \times 10^9/l$

WBC  $18 \times 10^9/l$

Blood film Left shifted neutrophils in large numbers

Na<sup>+</sup> 142 mmol/l

K<sup>+</sup> 4.1 mmol/l

Urea 6 mmol/l

Creatinine 90  $\mu$ mol/l

Bilirubin 23  $\mu$ mol/l

ALP 170 u/l

ALT 50 u/l

Albumin 35 g/l

What is the most appropriate first line treatment?

[Azithromycin18%Chloroquine9%Doxycycline53%Mefloquine10%Supportive medications10%](#)

This lady has a triad of fever, hepatosplenomegaly and encephalitis, which in a returning traveller could point towards a number of diseases including malaria and dengue fever. However, the lesion on her shin is an eschar, which points towards a diagnosis of rickettsia. Given her clinical signs and that she has been to Indonesia, this is likely to be scrub typhus (infection with *Orientia Tsutsugamushi*). Low platelets, raised LFTs and bilateral infiltrates on chest x-ray support this diagnosis.

First line treatment is with doxycycline for seven days, although a single dose of azithromycin may work in those for whom it is not possible to give doxycycline.

Mefloquine and Chloroquine are used in malaria. Supportive therapy is the recommended treatment in dengue fever.

## **Typhus**

### Overview

- rickettsial diseases
- transmitted between hosts by arthropods
- cause widespread vasculitis

#### Features

- fever, headache
- black eschar at site of original inoculation
- rash e.g. maculopapular or vasculitis
- complications: deranged clotting, renal failure, DIC

#### Rocky Mountain spotted fever

- caused by *R. rickettsii*
- initially macular rash on hands and feet then spreads

#### Tick typhus

- caused by *R. conorii*
- rash initially in axilla then spreads

#### Question 2 of 74

A 30 year old home aquarium enthusiast presents with multiple swellings tracking up his right arm. He states that the swellings have appeared over the course of 3-4 weeks. On examination he systemically appears well, he has multiple painless fluctuating nodules approximately 1cm in diameter tracking up his right arm. Which organism is responsible for the features described?

[\*Mycobacterium aquarium\*25%](#)[\*Mycobacterium bovis\*5%](#)[\*Mycobacterium tuberculosis\*5%](#)[\*Mycobacterium avium intracellulare\*11%](#)[\*Mycobacterium marinum\*55%](#)

The disease in question is fish tank granuloma (also known as aquarium granuloma).

*Mycobacterium avium intracellulare* (also known as *Mycobacterium avium* complex) is often associated with AIDS. It is a NON tuberculosis causing organism.

*Mycobacterium bovis* is the cause of Bovine tuberculosis, it rarely infects humans, but if it does, it is usually via the consumption of unpasteurised milk.

There is no such organism as *Mycobacterium aquarium*.

It is expected that candidates have heard of *Mycobacterium tuberculosis* already!

## *Mycobacterium marinum*

*Mycobacterium marinum* is one of many mycobacteria that can cause disease in humans. Fish tank granuloma typically presents in patients who have had an exposure to, or frequently work with fish. It has an incubation period of 3-4 weeks and lesions can be painful or painless. A cut or break in the skin can be enough for the organism to enter the blood stream and track up the lymphatic system (sporotrichoid spread). Treatment options include tetracyclines, fluoroquinolones, sulfonamides and macrolides.

### Question 3 of 74

A 46 year old Indian gentleman who moved to the UK four years previously presents to the Emergency Department complaining of a numb left foot. He has a background history of type 2 diabetes mellitus, hypertension and gastro-oesophageal reflux disease. His latest haemoglobin A1c (HbA1c) is 6.4%. On examination he has reduced sensation over the left heel and plantar aspect of the foot and six hypoesthetic, hypopigmented patches over both legs. What is the most appropriate management?

[Referral to diabetes specialist clinic for management of peripheral neuropathy8%Dapsone, clofazimine18%Rifampicin, clofazimine, isoniazid11%Rifampicin, dapsone, clofazimine50%Dapsone, terbinafine, rifampicin14%](#)

The travel history, the distribution of sensory peripheral loss and the pattern of hypoesthetic skin patches are the clues to this patient's diagnosis. *Mycobacterium leprae* is one of the most common causes of peripheral neuropathy worldwide and has a vast spectrum of presentations from the typical skin manifestations described here to systemic involvement involving the respiratory tract, kidneys, testes and bones.

When there is neurological involvement, the posterior tibial nerve is most commonly affected, (the pattern of sensory loss being described here) however there may equally be involvement of other nerves eg. ulnar, median, lateral popliteal and facial.

Although he may have some underlying diabetic peripheral neuropathy, the pattern of sensory loss would be symmetrical and therefore targeting treatment towards his diabetes will not necessarily help here.

For the treatment of multibacillary leprosy, the WHO have recommended a multi-drug therapy regimen of dapsone, rifampicin and clofazimine for a two year period.

## Leprosy

Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*.

### Features

- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

The degree of cell mediated immunity determines the type of leprosy a patient will develop.

Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')

- extensive skin involvement
- symmetrical nerve involvement

High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')

- limited skin disease
- asymmetric nerve involvement

### Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine

### Question 1 of 70

A 47-year-old man is referred by the emergency department with increasing shortness of breath. He is a known HIV patient managed by the local GUM consultants. He is not on any antiretroviral treatment. He presents with a two-week history of worsening shortness of breath. He is now breathless on minimal exercise. He has a non-productive cough and has felt lethargic for the last week. On examination he is afebrile, his blood pressure is 120/89 mmHg and he is slightly tachycardic at 110bpm. His respiratory rate is 18 at rest with saturations on 98% on air. When he mobilises to the toilet he becomes very tachypnoeic and his saturations drop to 90%.

His blood tests are as follows:

Hb 110 g/l  
Platelets  $201 \times 10^9/l$   
WBC  $9.6 \times 10^9/l$   
Neutrophils  $4.5 \times 10^9/l$

Na<sup>+</sup> 138 mmol/l  
K<sup>+</sup> 4.1 mmol/l  
Urea 7.8 mmol/l  
Creatinine 20  $\mu$ mol/l  
CRP 70 mg/l

Bilirubin 5  $\mu$ mol/l  
ALP 89 u/l  
ALT 43 u/l  
Albumin 34 g/l

An ABG is done which shows

pH 7.35  
pO<sub>2</sub> 7.7  
pCO<sub>2</sub> 4.6  
HCO<sub>3</sub><sup>-</sup> 21  
BE -3  
Lactate 2.2

His chest x-ray shows fine bilateral reticular nodular shadowing.

What is the most appropriate treatment to start in this gentleman?

[Tazocin4%Co-trimoxazole25%Aciclovir4%Co-trimoxazole and corticosteroids60%Highly active anti-retroviral treatment6%](#)

This gentleman is immunocompromised and has PCP. Patients with moderate to severe PCP should be treated with Co-trimoxazole and corticosteroids. Patients with mild to moderate PCP need only co-trimoxazole.

Mild:

- Breathlessness on mild exercise, which may be associated with a cough and sweats

- Arterial blood gases and oxygen saturation at rest, on air: PaO<sub>2</sub> >11 kPa; SaO<sub>2</sub> >96%
- Chest X-ray: normal or minor perihilar infiltrates

Moderate:

- Breathlessness on minimal exercise, fever (with or without sweats)
- Arterial blood gases and oxygen saturation at rest, on air: PaO<sub>2</sub> 8-11 kPa; SaO<sub>2</sub> 91-96%
- Chest X-ray: diffuse interstitial shadowing

Severe:

- Breathlessness at rest, persistent fever and cough
- Arterial blood gases and oxygen saturation at rest, on air: PaO<sub>2</sub> <8 kPa; SaO<sub>2</sub> <91%
- Chest X-Ray: extensive interstitial shadowing, with or without alveolar shadowing

## **HIV: *Pneumocystis jiroveci* pneumonia**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count < 200/mm<sup>3</sup> should receive PCP prophylaxis

Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

## Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

## Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if  $pO_2 < 9.3\text{kPa}$  then steroids reduce risk of respiratory failure by 50% and death by a third)



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

#### Question 2 of 70

A 28 year-old man presents to his doctor with a rash and bone pain. Radiographs of the limbs revealed numerous osteolytic lesions. He was successfully treated for secondary syphilis.

Which of the following tests is likely to remain positive in this patient despite treatment?

[Blood culture](#)4% [Treponema pallidum particle agglutination \(TPPA\)](#)42% [Venereal disease reference laboratory \(VDRL\)](#)35% [Rapid plasmin reagin \(RPR\)](#)12% [Wasserman test](#)7%

Syphilis is a disease caused by infection with the spirochete *Treponema pallidum*. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that *Treponema pallidum* cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis.

The *Treponema pallidum* particle agglutination assay (also called TPPA test) is an indirect agglutination assay used for detection and titration of antibodies against *Treponema pallidum*.

IgG antibodies to syphilis can remain elevated despite appropriate antimicrobial treatment and a reactive result does not distinguish between recent or past infection.

### Syphilis: investigation

*Treponema pallidum* is a very sensitive organism and cannot be grown on artificial media. The diagnosis is therefore usually based on clinical features, serology and microscopic examination of infected tissue

Serological tests can be divided into

- cardiolipin tests (not treponeme specific)
- treponemal specific antibody tests

#### Cardiolipin tests

- syphilis infection leads to the production of non-specific antibodies that react to cardiolipin



- examples include VDRL (Venereal Disease Research Laboratory) & RPR (rapid plasma reagin)
- insensitive in late syphilis
- becomes negative after treatment

#### Treponemal specific antibody tests

- example: TPHA (*Treponema pallidum* HaemAgglutination test)
- remains positive after treatment

#### Causes of false positive cardiolipin tests

- pregnancy
- SLE, anti-phospholipid syndrome
- TB
- leprosy
- malaria
- HIV



*Treponema pallidum*, the bacteria that cause syphilis. Note the spiral shape of the organism.  
Credit: NIAID

#### Question 3 of 70

A 41-year-old man with poorly controlled type 1 diabetes mellitus presents with a nodular lesion on the right-side of his face around the angle of the jaw. One month ago he had a tooth extraction at the dentist. The nodule is around 2 cm in diameter, raised and purple-red in colour. On examination a sinus tract is seen in the middle of the nodule which is draining a blood-stained fluid.

Microscopy of the discharge shows microscopic yellow granules.

What is the most likely causative organism?

[\*Actinomyces israelii\*56% \*Tunga penetrans\*17% \*Klebsiella\*8% \*Pseudomonas aeruginosa\*14% \*Escherichia coli\*4%](#)

## ***Actinomyces and Nocardia***

Both *Actinomyces* and *Nocardia* are Gram-positive rods that form fungus-like branched networks of hyphae-like filaments.

### ***Actinomyces israelii***

#### Basics

- chronic, progressive granulomatous disease caused by filamentous Gram-positive anaerobic bacteria from the *Actinomycetaceae* family.
- typically causes oral/facial abscesses with sulphur granules in sinus tracts
- may also cause an abdominal mass e.g. in the right iliac fossa

*Actinomyces* are commensal bacteria that become pathogenic when a mucosal barrier is breached.

The disease most commonly occurs in the head and neck, although it may also occur in the abdominal cavity and in the thorax.

The mass will often enlarge across tissue planes with the formation of multiple sinus tracts.

Abdominopelvic actinomycosis occurs most frequently in individuals that have had appendicitis (65%).

#### Pathology

- On histological examination Gram-positive organisms and evidence of sulphur granules.
- Sulphur granules are colonies of organisms that appear as round or oval basophilic masses.
- They are also seen in other conditions such as nocardiosis

#### Treatment

- Long-term antibiotic therapy usually with penicillin
- Surgical resection is indicated for extensive necrotic tissue, non-healing sinus tracts, abscesses or where biopsy is needed to exclude malignancy.

## References

Wong V, Turmezei T and Weston V. Actinomycosis. *BMJ* 2011;343d6099.

## *Nocardia*

### Basics

- typically causes pneumonia in immunocompromised patients
- may also cause brain abscesses

### Question 4 of 70

A 23-year-old man presents for the second time to HIV clinic. He was found to have positive HIV serology on opportunistic screening in a local GUM clinic and was referred to HIV services. He had originally presented with dysuria and had been diagnosed with non-specific urethritis and treated with doxycycline. Following his diagnosis, he has separated with his partner, as she feared contracting HIV from him. He is anxious with managing his disease and is keen to start treatment. He has no other symptoms, feeling systemically well and no significant past medical history.

During his previous consultation, his diagnosis was discussed with him, and the role of antiretroviral treatment was fully explained.

### Blood tests:

Hb	134 g/l
Platelets	$378 \times 10^9/l$
WBC	$7.2 \times 10^9/l$
Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	4.1 mmol/l
Urea	4.6 mmol/l
Creatinine	64 $\mu$ mol/l
HIV viral load	223 copies/ml
CD4 count	914 cells/mm <sup>3</sup>

What is the most appropriate management plan offer?

[Start antiretroviral therapy and PCP prophylaxis11%](#)[Start antiretroviral therapy72%](#)[Start treatment when CD4 count becomes <3507%](#)[Start treatment when CD4 count becomes <5505%](#)[Start treatment once HIV related symptoms develop4%](#)

This is a patient with newly diagnosed HIV and should be offered HIV treatment regardless of CD4 count or viral load. PCP prophylaxis is only necessary when the CD4 count becomes much lower.

Source:

'BHIVA Guidelines for the Treatment of HIV-1-positive Adults with Antiretroviral Therapy 2015.' BHIVA. , Aug. 2016.

### **HIV: *Pneumocystis jiroveci* pneumonia**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count < 200/mm<sup>3</sup> should receive PCP prophylaxis

#### Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

#### Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

## Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if  $pO_2 < 9.3\text{kPa}$  then steroids reduce risk of respiratory failure by 50% and death by a third)



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

You are the medical basic specialist trainee on call and have been asked to see a gentleman who has just been admitted for a bad chest infection. According to the ward nurse, he has developed an allergic reaction after five minutes of vancomycin i.v infusion.

On arrival you proceed to examine this young man who is febrile, obviously unwell and receiving oxygen via nasal prongs. He claims he had not developed any new symptoms since admission but felt sudden warmth and flushing few minutes into his vancomycin drip. On examination he has crepitations in his left base.

Apart from generalised erythema he appears to be stable and there is no immediate danger to his airways. His blood pressure was 105/67mmHg, pulse was 99b/min and oxygen saturation on 4L oxygen was 95% (all observations are similar to previous readings). He has never taken vancomycin but states he is allergic to penicillin and ciprofloxacin.

Given the likely diagnosis, what is the next step in your management?

[Immediately stop vancomycin9%Continue vancomycin but at a slower rate68%Continue vancomycin rate unchanged5%Administer i.v chlorphenamine maleate and stop vancomycin13%Urgent i.m adrenaline4%](#)

Answer: continue vancomycin but at a slower rate.

This is typical red man syndrome caused by rapid infusion of vancomycin i.v. Vancomycin should be administered diluted and at a rate of 10mg/minutes for doses over 500mg i.v.

It is an IgE independent mast cell degranulation reaction that occurs up to 10 minutes into receiving vancomycin i.v at a fast rate. It is not a true allergic reaction thus vancomycin should be continued but at a lower rate of infusion.

Antihistamine prophylaxis, lower but frequent dosing and 2 hour infusion rate have been found to reduce the incidence of red man syndrome.

This gentleman is obviously unwell but his vitals and chest findings are more in keeping with his chest infection and possible sepsis.

Red-man syndrome after vancomycin: potential cross-reactivity with teicoplanin C Khurana, M A de Belder <http://pmj.bmj.com/content/75/879/41.long>

## **Vancomycin**

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).

### Mechanism of action

- inhibits cell wall formation by binding to D-Ala-D-Ala moieties, preventing polymerization of peptidoglycans

### Mechanism of resistance

- alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits (normally D-alanyl-D-alanine) to which the antibiotic binds

### Adverse effects

- nephrotoxicity
- ototoxicity
- thrombophlebitis
- red man syndrome; occurs on rapid infusion of vancomycin

### Question 1 of 74

A 21-year-old male presents on the medical take with fever, rigors and a headache which started yesterday. He returned from a 2 week trip travelling across south east Asia 5 days ago. His last destination was Bangkok and prior to this he had been in the mostly rain forested area of northern Thailand. His symptoms started around 5 days after arriving in Thailand.

He did not take malaria prophylaxis during the trip but had received all the recommend vaccinations. He travelled with his long-term girlfriend and he reports always using condoms during intercourse.

On examination he has a fever of 38.9°C, a pulse of 92 beats per minute, blood pressure of 115/80 mmHg, oxygen saturations of 99% on air. There is an area of confluent blanching erythema over the precordium and fundoscopy was poorly tolerated due to pain.

What is the most likely diagnosis?

[Dengue fever51% HIV seroconversion7% Malaria15% Typhoid19% Infectious mononucleosis7%](#)

This questions examines your knowledge of incubation times. Dengue fever is endemic in south east Asia and is transmitted by the mosquito *Aedes Aegypti* . This mosquito resides in urban areas and uses puddles and open water tanks to breed in. The incubation period for dengue is 4-10 days. The clinical presentation is often non-specific however classically there is a retrobulbar headache and a confluent erythematous rash over the precordium associated with a high fever.



Management is generally supportive with the main complication being a fall in platelets and transformation into the virulent haemorrhagic form.

HIV is a plausible option given the presentation but the incubation period does not fit. Remember his symptoms started 5 days after arriving in Thailand. Seroconversion generally presents with symptoms between one and three weeks post exposure and given that he used protective measures this makes HIV unlikely.

Malaria is unlikely for similar reasons, the incubation period for *P.falciparum* malaria is usually 7 days. In addition SE Asia is not endemic for malaria and dengue fever would be much more likely.

Typhoid has an incubation period of 5-21 days after consuming the causative microorganism. Classically it presents in week one with a high fever, relative bradycardia or pulse-temperature dissociation. In week two there is development of abdominal pain and rose spots. If still untreated by week 3 hepatosplenomegaly can develop as well as gut perforation secondary to the hyperproliferation of gut Peyer's patches.

Infectious mononucleosis fits with the clinical presentation but has an incubation period of between 4-8 weeks making this an unlikely diagnosis.

## **Dengue fever**

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

### **Basics**

- transmitted by the *Aedes aegypti* mosquito
- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

### **Features**

- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain

- facial flushing (dengue)
- maculopapular rash

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

#### Question 1 of 65

A 17 year old girl presents to A&E accompanied by her anxious mother. She was born in England, but both her parents were born in a rice growing community in rural China. She has recently returned from a holiday where she was visiting her family in China. They live on a farm where she had close contact with dogs, sheep and pigs.

She arrived home one week ago. She was taking Mefloquine for malaria prophylaxis.

She was complaining of fever and a headache yesterday. Today she has been confused and disorientated.

She is previously fit and well, she has had all her immunisations according to the UK immunisation schedule, with normal growth and development. She does well at college and is a keen member of her college canoe club. She has no allergies.

On examination she is febrile at 38.9°C but haemodynamically stable. She appears confused and has an obvious difficulty walking. Examination of her cranial nerves is difficult but unremarkable. She has normal power and increased tone in her arms, which is more pronounced on the left side, with hyperreflexia bilaterally. She has several writhing involuntary movements of her upper limbs during the consultation.

A CT scan shows hypodensity in the thalami and basal ganglia bilaterally, more pronounced on the left side.

A lumbar puncture reveals a lymphocytic CSF with a raised protein.

What is the most likely diagnosis?

[Herpes Simplex Encephalitis 12%](#)[Japanese Encephalitis 70%](#)[Alcohol consumption 3%](#)[Rabies 10%](#)[Mefloquine toxicity 6%](#)

#### **Japanese encephalitis**

Japanese encephalitis is the most common cause of viral encephalitis in South East Asia, China the Western Pacific and India, with approx. 50,000 cases annually. It is a flavivirus transmitted by culex mosquitos which breeds in rice paddy fields. The reservoir hosts are aquatic birds, but pigs are an amplification host and therefore close domestic contact with pigs is a risk factor.

The majority of infection is asymptomatic.

Clinical features are headache, fever, seizures. Parkinsonian features indicate basal ganglia involvement. It can also present with acute flaccid paralysis.

Diagnosis is by serology or PCR. Management is supportive.

Prevention is a vaccine and there are a variety of different types.

#### Question 2 of 65

As the doctor on call you are called to review a 28-year-old male on the haematology ward. He recently underwent an allogenic stem cell transplant, which so far had been reasonably uncomplicated. Earlier in the week the patient had complained of coryzal symptoms and a dry cough. A nasopharyngeal aspirate (NPA) had been sent along with other routine tests 24 hours ago.

When you arrive to review the patient on the ward you note that he appears extremely sweaty. You take his temperature using a tympanic thermometer which reads 39.5°C. His heart rate is 95 beats per minute and his respiratory rate is 16 breaths per minute. Blood pressure is 122/76 mmHg. Physical examination is unremarkable and chest X-ray reveals clear lung fields.

You review the patients most recent results:

Hb	95 g/l	Na <sup>+</sup>	134 mmol/l
Platelets	50 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.6 mmol/l
WBC	0.1 * 10 <sup>9</sup> /l	Urea	3.0 mmol/l
Neuts	0.1 * 10 <sup>9</sup> /l	Creatinine	65 µmol/l
Lymphs	0.0 * 10 <sup>9</sup> /l	CRP	12 mg/l
Eosin	0.0 * 10 <sup>9</sup> /l		
NPA	Influenza A		

What is the most appropriate treatment to commence?

[Amoxicillin5%Oseltamivir54%No treatment required7%Flucloxacillin5%Zanamivir28%](#)

In this case the key points to realise are that the patient is immunosuppressed (neutropaenic post transplant) with symptoms and PCR confirmed Influenza A infection.

Whilst in most cases, oseltamivir (a neuraminidase inhibitor) is first line treatment for influenza, the BNF advises that for severely immunocompromised individuals zanamivir should be first line treatment. This can help reduce the length of symptoms and prevent complications from developing during the course of the infection.

## Antiviral agents

Drug	Mechanism of action	Indications	Adverse effects/toxicity
<b>Aciclovir</b>	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	HSV, VZV	Crystalline nephropathy
<b>Ganciclovir</b>	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	CMV	Myelosuppression/agranulocytosis
<b>Ribavirin</b>	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA	Chronic hepatitis C, RSV	Haemolytic anaemia
<b>Amantadine</b>	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech
<b>Oseltamivir</b>	Inhibits neuraminidase	Influenza	
<b>Foscarnet</b>	Pyrophosphate analog which inhibits viral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnasaemia, seizures
<b>Interferon-<math>\alpha</math></b>	Human glycoproteins which inhibit synthesis of mRNA	Chronic hepatitis B & C, hairy cell leukaemia	Flu-like symptoms, anorexia, myelosuppression
<b>Cidofovir</b>	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and	CMV retinitis in HIV	Nephrotoxicity

Drug	Mechanism of action	Indications	Adverse effects/toxicity
	contrast with aciclovir/ganciclovir)		

### Anti-retroviral agent used in HIV

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine

Protease inhibitors (PI)

- inhibits a protease needed to make the virus able to survive outside the cell
- examples: indinavir, nelfinavir, ritonavir, saquinavir

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz

### Question 3 of 65

A 22-year-old Ethiopian female presents on the medical take with an exacerbation of asthma. She has been treated for asthma since her late teens and has generally been well controlled with PRN salbutamol alone and has never required steroids or hospital admission.

She became increasingly breathless 3 days ago and visited her GP who prescribed prednisolone and amoxicillin. However her symptoms have worsened considerably and her FEV1 is now 55% her expected value.

On examination she has a temperature of 37.5°C, a heart rate of 92 beats per minute, a blood pressure of 118/76 mmHg and respiratory rate of 22/min. There is diffuse wheeze across across the chest. You also notice excoriations over the skin from intense scratching.

Investigations:

haemoglobin 102 g/L (130-180)  
white cell count 5.4 X 10<sup>9</sup>/L (4.0-11.0)  
eosinophil count 0.78 X 10<sup>9</sup>/L (0.04-0.40)  
platelet count 478 X 10<sup>9</sup>/L (150-400)

CXR                      diffuse patchy infiltrates

What is the most appropriate management?

[Ivermectin and PRN salbutamol nebulisers55%IV Hydrocortisone and PRN salbutamol nebulisers16%IV Antibiotics with PO prednisolone and PRN salbutamol10%IV antibiotics until stable then antiretroviral therapy6%Discuss with ITU with a view to transferring care12%](#)

The diagnosis here is strongyloidiasis. When the skin comes into contact with filariform larvae found in soil contaminated with faeces, it migrates haematogenously to the lungs where it invades the alveolar space and enters the bronchial tree. Here it causes irritation and a dry cough before the larvae are swallowed. In the duodenum and jejunum the larvae develop into adults producing more larvae that can also directly invade the bowel wall (auto-infection) or be excreted through faeces.

Adult worms can live for many years without causing any symptoms as they do not stimulate an immune response. However if the body becomes immunosuppressed then auto-infection occurs more readily and can lead to disseminated disease. This can cause a 'larva currens' picture which results in intense pruritus as worms migrate through the skin. In asthmatics immunosuppression with steroids causes a paradoxical worsening of symptoms as increased numbers of larvae migrate through the lungs and are swallowed.

The patchy infiltrates are further suggestive of disseminated strongyloidiasis but could also represent PCP pneumonia in an immunocompromised host. However there is nothing further in the history to suggest that she has HIV. As a result we can explain the chest x-ray appearance with a diagnosis of strongyloidiasis therefore removing the need for antibiotics or antiretrovirals.

Her asthma signs do not warrant classification in the severe category so discussion with ITU is not warranted.

### ***Strongyloides stercoralis***

*Strongyloides stercoralis* is a human parasitic nematode worm. The larvae are present in soil and gain access to the body by penetrating the skin. Infection with *Strongyloides stercoralis* causes strongyloidiasis.

#### Features

- diarrhoea
- abdominal pain/bloating

- papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

## Treatment

- ivermectin and albendazole are used

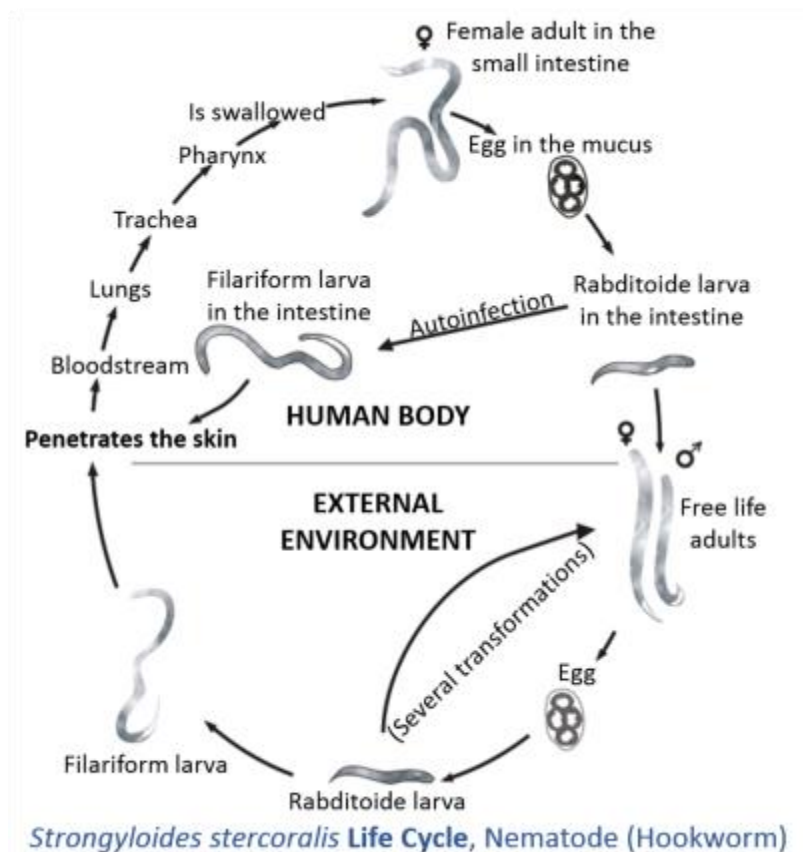


Image sourced from [Wikipedia](#)

Diagram showing the lifecycle of *Strongyloides stercoralis*

## Question 1 of 61

A 44-year-old businessman was admitted to the general medical take with fever, jaundice and headaches. He had returned from a business trip in Hong Kong one month ago. He is a keen river sailor and has been unable to sail for the last two weeks.

On examination he is tachycardic with temperature of 39.5°C. He appears confused and is combative during the examination. His chest has scattered crackles bibasally with some right upper quadrant abdominal pain

### Investigations

Hazy lung infiltrates bibasally

Haemoglobin 135 g/L (130-180)

White cell count  $17.8 \times 10^9/L$  (4.0-11.0)

Neutrophil count  $15.7 \times 10^9/L$  (1.5-7.0)

Platelet count  $413 \times 10^9/L$  (150-400)

Serum C-reactive protein 345 mg/L (<10)

Serum urea 13.3 mmol/L (2.5-7.0)

Serum total bilirubin 110 mol/L (122)

Serum alanine aminotransferase 117 U/L (535)

Serum alkaline phosphatase 110 U/L (45-105)

Chest X-Ray Serum gamma glutamyl transferase 61 U/L (<50)

X-Ray What is the most likely diagnosis?

[Dengue Fever 9% HIV seroconversion 8% Acute hepatitis A 13% Malaria 7% Leptospirosis 63%](#)

Leptospirosis is the most likely diagnosis. The river sailing puts this gentleman at risk of contact with contaminated water from animal urine. Incubation is between 4-14 days. Typical symptoms include high fever, headache, muscle aches, vomiting and may have meningitis and jaundice.

Hong Kong is not a malaria endemic region nor is it a common region for Dengue Fever. HIV seroconversion would not explain jaundice or deranged liver function. Acute Hepatitis A infection is prevalent in Hong Kong and incubation period is between 2 - 6 weeks but infection would not explain the neurological symptoms.

### Leptospirosis

Also known as Weil's disease\*, leptospirosis is commonly seen in questions referring to sewage



workers, farmers, vets or people who work in abattoir. It is caused by the spirochaete *Leptospira interrogans* (serogroup L icterohaemorrhagiae), classically being spread by contact with infected rat urine. Weil's disease should always be considered in high-risk patients with hepatorenal failure

#### Features

- fever
- flu-like symptoms
- renal failure (seen in 50% of patients)
- jaundice
- subconjunctival haemorrhage
- headache, may herald the onset of meningitis

#### Management

- high-dose benzylpenicillin or doxycycline

\*the term Weil's disease is sometimes reserved for the most severe 10% of cases that are associated with jaundice

#### Question 2 of 61

A 40-year-old gentleman was admitted with fever, dry cough, headache, abdominal pain and diarrhoea. Around ten days previously he had been complaining of intermittent fevers and night sweats but otherwise felt well. In the last 3 days, he had developed generalised abdominal pain and watery diarrhoea, along with a dry cough and headache. Prior to this he had felt constipated only having opened his bowels once in three days which he thought was unusual as he had eaten a large amount of fruit off the market stools in South Korea where he had recently been on a business trip.

On examination, he was notably jaundiced, had a macular rash over his chest and had tender hepatomegaly. Observations revealed a temperature of 40.1°C, heart rate 38/min, regular and a blood pressure of 130/90 mmHg. ECG showed a sinus bradycardia.

Blood tests revealed:

WBC	14.0 * 10 <sup>9</sup> /l
Neutrophils	12.0 * 10 <sup>9</sup> /l
CRP	230 mg/l
Bilirubin	52 µmol/l
ALP	80 u/l

ALT            200 u/l  
Albumin      32 g/l

What investigation would you do to obtain the diagnosis?

[Blood cultures 53% Abdominal ultrasound 22% HIV test 12% Lumbar puncture 8% ECG 5%](#)

Typhoid or enteric fever is the commonest serious tropical disease requiring treatment from Asia. Incubation period 7-18 days (range: 3-60 days). The highest incidence is found in south-central Asia and south-east Asia.

Patients most commonly present with fever, headache, constipation/diarrhoea, malaise, anorexia, dry cough, abdominal pain, hepatosplenomegaly, Rose spot rash, bradycardia and potentially misleading symptoms including meningism may occur.

Transmission is usually from contaminated food or water, occasionally direct faecal-oral transmission, shellfish taken from sewage-polluted areas, ingestion of contaminated milk and milk products and flies may cause human infection through the transfer of infectious agents to foods. Around 25% of those who contract typhoid fever become chronic carriers, as bacteria persist in the biliary tract after symptoms have resolved.

Investigations may reveal raised WCC, deranged LFTS. Blood cultures have the highest yield within the first week of symptoms (sensitivity 40-80%). Diagnosis can also be made from stool and urine cultures (become positive after the first week) and bone marrow cultures.

Treatment is with quinolones most commonly ciprofloxacin. However, there has been increasing reports of quinolones resistance in patients returned from Asia and intravenous ceftriaxone may be used. If quinolone resistance is confirmed azithromycin or cefixime are suitable oral alternatives for uncomplicated disease. Treatment should be continued for 14 days to reduce the risk of relapse. The addition of steroids may be helpful in severe cases

Complications can include GI bleeding, intestinal or biliary perforation, acalculous cholecystitis, pneumonia, myocarditis, pancreatitis, UTIs, osteomyelitis, meningitis and typhoid encephalopathy,

## ***Salmonella***

The *Salmonella* group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi* (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, arthralgia

#### Features

- initially systemic upset as above
- relative bradycardia
- abdominal pain, distension
- constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid
- rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

#### Possible complications include

- osteomyelitis (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%, more likely if adult females)

#### Question 3 of 61

A 46-year-old woman presents with a 4 week history of cough. This is non-productive and not associated with dyspnoea or chest pain. The symptoms were preceded by a 'head cold'. Her past medical history includes asthma as a child and smoking. Respiratory examination reveals a clear chest with no added sounds. Oxygen saturations are 98% on room air. Temperature is 36.7°C and heart rate 72/min.

A chest x-ray is requested as she is a smoker:



© Image used on license from [Radiopaedia](#)

What is the most likely explanation for the changes on the x-ray?

[Healed varicella pneumonia 45%](#) [Idiopathic pulmonary fibrosis 8%](#) [Cryptogenic organizing pneumonia 17%](#) [Tuberculosis 13%](#) [Sarcoidosis 17%](#)

The chest x-ray shows miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

## Chickenpox

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion

Chickenpox is highly infectious

- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared\*
- incubation period = 10-21 days

Clinical features (tend to be more severe in older children/adults)

- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management is supportive

- keep cool, trim nails
- calamine lotion
- school exclusion\*: children should be kept away from school for at least 5 days from onset of rash (and not developing new lesions)
- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered

A common complication is secondary bacterial infection of the lesions. Rare complications include

- pneumonia
- encephalitis (cerebellar involvement may be seen)
- disseminated haemorrhagic chickenpox
- arthritis, nephritis and pancreatitis may very rarely be seen



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Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

\*the official advice regarding school exclusion for chickenpox has gone back and forth over recent years. In September 2017 Public Health England advocated the 5 day rule:

*Children should be kept away from school for at least 5 days from onset of rash (and not developing new lesions). It is not necessary for all the spots to have healed or crusted over before return to school as the risk of transmission to other children after 5 days is minimal.*

<https://www.gov.uk/government/publications/health-protection-in-schools-and-other-childcare-facilities/chapter-9-managing-specific-infectious-diseases#chicken-pox-shingles>

A 20-year-old woman who is 16 weeks pregnant presents with pain passing urine and an irritating rash. On examination, she has a tender, red, vesicular rash on her vulva. A urine dipstick shows both blood and white cells. What is the best treatment?

[Clotrimazole11%Cefalexin12%Oral aciclovir47%Topical aciclovir23%Fluconazole6%](#)

This patient has genital herpes simplex virus (HSV). The guidelines recommend treatment with oral (or intravenous) aciclovir at any stage in pregnancy. Aciclovir is not licensed in pregnancy but is considered safe and not associated with birth defects. It is well tolerated in pregnancy. Paracetamol and topical lidocaine 2% gel can be used for symptomatic relief.

The primary purpose of treatment is to reduce the risk of transmission to the neonate at birth. The risk is much more considerable with primary genital herpes simplex within the final six weeks of pregnancy. Caesarian section should be the recommended mode of delivery for all women developing the first episode of genital HSV in the third trimester.

<https://www.rcog.org.uk/globalassets/documents/guidelines/management-genital-herpes.pdf>

## **Herpes simplex virus**

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

### **Features**

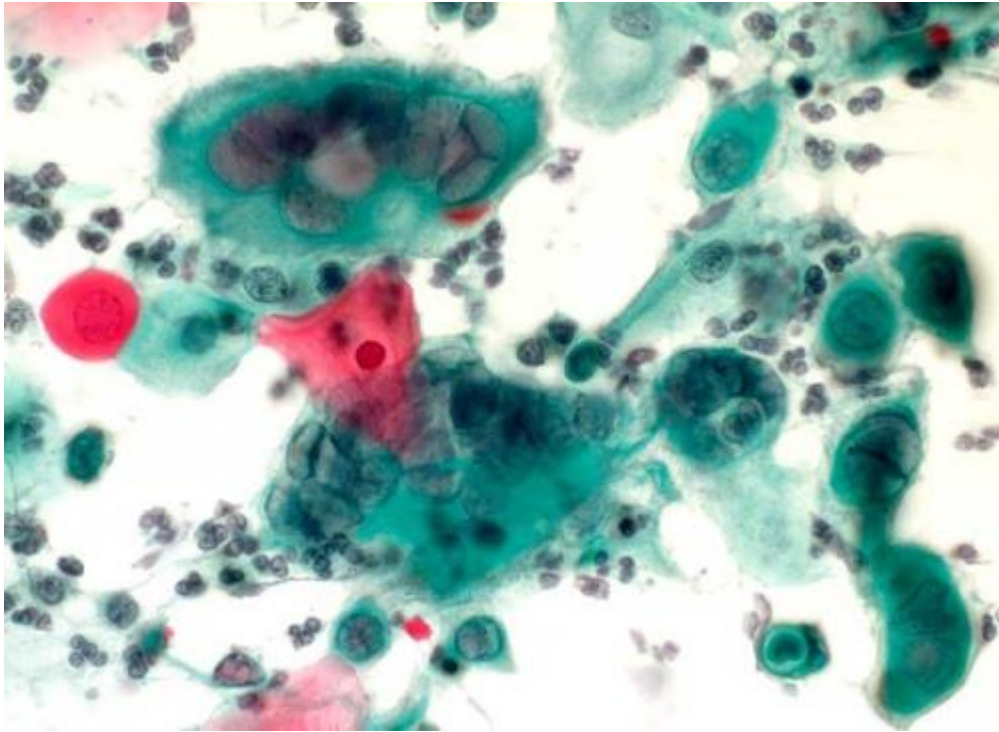
- primary infection: may present with a severe gingivostomatitis
- cold sores
- painful genital ulceration

### **Management**

- gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest
- genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

### **Pregnancy**

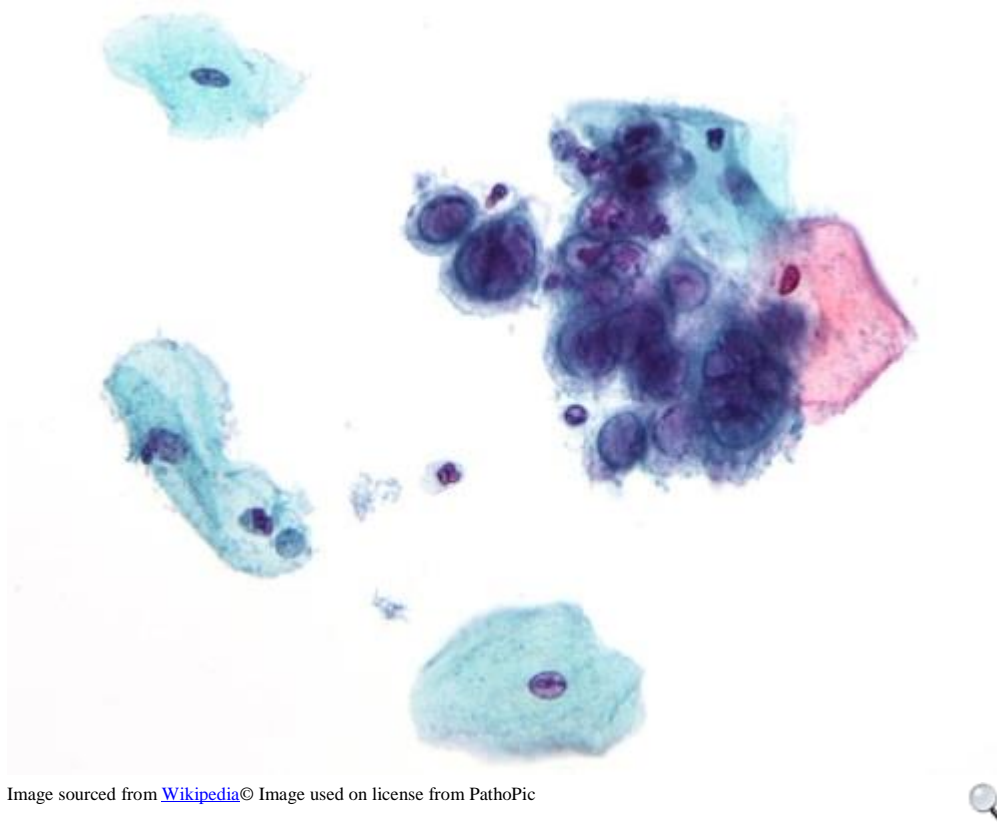
- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation
- women with recurrent herpes who are pregnant should be treated with suppressive therapy and be advised that the risk of transmission to their baby is low



© Image used on license from PathoPic

Pap smear. Multinucleated giant cells representing infection by the herpes simplex virus. Note the 3 M's; Multinucleation, Margination of the chromatin, Molding of the nuclei





Further Pap smear showing the cytopathic effect of HSV (multi-nucleation, ground glass & margined chromatin)

#### Question 1 of 56

A 34 year-old man from South Korea presents with a two week history of abdominal pain in the right upper quadrant, fever and weight loss. The pain does not radiate anywhere and is 6/10 on the pain scale. Apart from the above he has no other symptoms. His only family history is his father who has hepatitis B and HIV. Examination reveals a 3cm tender palpable liver edge, pyrexia of 38.9°C, pallor and right upper quadrant pain. There is no jaundice.

Blood tests reveal:

Bilirubin 29  $\mu\text{mol/l}$

ALP 200 u/l

ALT 90 u/l

$\gamma\text{GT}$  100 u/l

Albumin 38 g/l

An ultrasound scan is requested and shows a 3x3cm abscess in the right lower lobe of the liver.

The liver abscess is subsequently aspirated. Apart from aspiration of the large liver abscess, what is the most appropriate treatment?

[Blood cultures8%](#) [Karyotyping5%](#) [Metronidazole treatment54%](#) [Liver biopsy4%](#) [Mebendazole treatment29%](#)

The most likely diagnosis in this case is an amoebic abscess, which are normally found in endemic tropical countries. Aspiration of large liver abscesses and a course of metronidazole is the preferred treatment for this condition.

## Amoebiasis

Amoebiasis is caused by *Entamoeba histolytica* (an amoeboid protozoan) and spread by the faecal-oral route. It is estimated that 10% of the world's population is chronically infected. Infection can be asymptomatic, cause mild diarrhoea or severe amoebic dysentery. Amoebiasis also causes liver and colonic abscesses

### Amoebic dysentery

- profuse, bloody diarrhoea
- stool microscopy may show trophozoites
- treatment is with metronidazole

### Amoebic liver abscess

- usually a single mass in the right lobe (may be multiple)
- features: fever, RUQ pain
- serology is positive in > 90%

## Question 2 of 56

A 53-year-old lady comes into the Emergency Department with a cough productive of green sputum and palpitations. She feels very unwell, feverish and lethargic. On examination, she has bronchial breathing at her right base with respiratory rate 25/min, sats 95% on room air. Her heart sounds are normal with an irregularly irregular heartbeat. Her heart rate was 120/min and blood pressure 90/40 mmHg. An ECG shows atrial fibrillation with a fast ventricular rate. She has no history of atrial fibrillation. What is the first treatment that should be given for her atrial fibrillation?

[Bisoprolol10%Digoxin8%Intravenous fluids57%Oral antibiotics15%Flecainide11%](#)

This patient is clearly septic from pneumonia. This has tipped the patient into atrial fibrillation (AF) given there is no previous history of atrial fibrillation. It is important to treat the sepsis as the cause of the AF. To do this it is imperative to give IV fluids and IV antibiotics. If the patient's AF does not settle following the resolution of the sepsis then other options would be considered.

## Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection. Sepsis is increasingly recognised as an important cause of mortality in the UK and there has been increasing efforts recently to improve the care of patients who present with sepsis.

How sepsis is classified has changed in recent years - the Surviving Sepsis Guidelines were updated in 2017.

The new guidelines recognise the following terms:

- **sepsis:** life-threatening organ dysfunction caused by a dysregulated host response to infection
- **septic shock:** a more severe form sepsis, technically defined as *'in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone'*\*

The old category of severe sepsis is no longer used.

The term 'systemic inflammatory response syndrome (SIRS)' has also fallen out of favour. Adult patients outside of ICU with suspected infection are identified as being at heightened risk of mortality if they have quickSOFA (qSOFA) score meeting  $\geq 2$  of the following criteria: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100mmHg or less

## Management

NICE released their own guidelines in 2016. These focussed on the risk stratification and management of patients with suspected.

For risk stratification NICE recommend using the following criteria:

### Red flag criteria

- Responds only to voice or pain/ unresponsive
- Acute confusional state
- Systolic B.P  $\leq 90$  mmHg (or drop  $>40$  from normal)
- Heart rate  $> 130$  per minute
- Respiratory rate  $\geq 25$  per minute
- Needs oxygen to keep SpO<sub>2</sub>  $\geq 92\%$
- Non-blanching rash, mottled/ ashen/ cyanotic
- Not passed urine in last 18 h/ UO  $< 0.5$  ml/kg/hr
- Lactate  $\geq 2$  mmol/l
- Recent chemotherapy

### Amber flag criteria

- Relatives concerned about mental status
- Acute deterioration in functional ability
- Immunosuppressed
- Trauma/ surgery/ procedure in last 6 weeks
- Respiratory rate 21-24
- Systolic B.P 91-100 mmHg
- Heart rate 91-130 OR new dysrhythmia
- Not passed urine in last 12-18 hours
- Temperature  $< 36^{\circ}\text{C}$
- Clinical signs of wound, device or skin infection

Clearly the underlying cause of the patients sepsis needs to be identified and treated and the patient supported regardless of the cause or severity. If however any of the red flags are present the 'sepsis six' should be started straight away:

1. Administer oxygen: Aim to keep saturations  $> 94\%$  (88-92% if at risk of CO<sub>2</sub> retention e.g. COPD)
2. Take blood cultures
3. Give broad spectrum antibiotics
4. Give intravenous fluid challenges: NICE recommend a bolus of 500ml crystalloid over less than 15 minutes
5. Measure serum lactate
6. Measure accurate hourly urine output

\*these patients can be clinically identified by a vasopressor requirement to maintain a MAP  $\geq 65$ mmHg and serum lactate  $> 2$ mmol/L in the absence of hypovolemia

### Question 3 of 56

A 65-year-old man has just returned from a trip to India one week ago. He has had bloody diarrhoea and fevers for the last two weeks and noted rose coloured spots on his abdomen yesterday. Apart from a prosthetic aortic valve, he has no significant past medical history. His blood tests indicate raised inflammatory markers and stool microbiology has found a gram-negative bacillus identified as a non-typhoidal *Salmonella*. Sensitivities are pending. Which one of the following options is best initial empiric management?

[Amoxicillin + clavulanic acid8%Gentamicin7%Ciprofloxacin66%Clindamycin9%Not for antibiotics10%](#)

According to the NICE guidelines, anyone above the age of 50, immunocompromised or has cardiac valve disease/endovascular abnormalities should be treating empirically with

ciprofloxacin 500mg BD when they have been diagnosed with non-typhoidal *Salmonella* gastroenteritis.

For more information please click on the link to the NICE CKS on gastroenteritis  
<http://cks.nice.org.uk/gastroenteritis#!scenario:2>

## ***Salmonella***

The *Salmonella* group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi* (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, arthralgia

### Features

- initially systemic upset as above
- relative bradycardia
- abdominal pain, distension
- constipation: although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid
- rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

### Possible complications include

- osteomyelitis (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%, more likely if adult females)

### Question 4 of 56

A young 27 year-old man who has been travelling on a jungle expedition across south east Asia presents to the local doctors with a 3 day history of fever, headache and a widespread maculopapular rash. He has been kayaking through rivers, trekking through long grass and

jungle, and he reports being bitten by mosquitos, flies and mites. On close inspection he has a black necrotic eschar on his leg. A malaria rapid diagnostic test (RDT) is negative.

What is the most appropriate management?

[Artemether / lumefantrine 8% Benzylpenicillin 12% Corticosteroids 5% Doxycycline 65% Supportive care 11%](#)

The history describes a classical case of scrub typhus - and in particular the black eschar is the key diagnostic clue. Scrub typhus is caused by the tropical rickettsial bacteria *Orientia tsutsugamushi* and is transmitted by the bite of an infective trombiculoid 'chigger' mite. Its distribution is limited to South East Asia. Complications of disease include jaundice, meningoencephalitis, myocarditis, pneumonia and renal failure. However the disease can be easily treated with doxycycline.

Similar disease presentations are seen in other continents. *Rickettsia rickettsii* causes the potentially fatal Rocky Mountain spotted fever (RMSF), but its distribution is limited to North and Central America. African tick typhus is a mild and self limiting infection with no reported deaths and caused by *R. africae*. Other tropical rickettsial disease include endemic murine typhus and epidemic louse borne typhus which are more serious forms of disease.

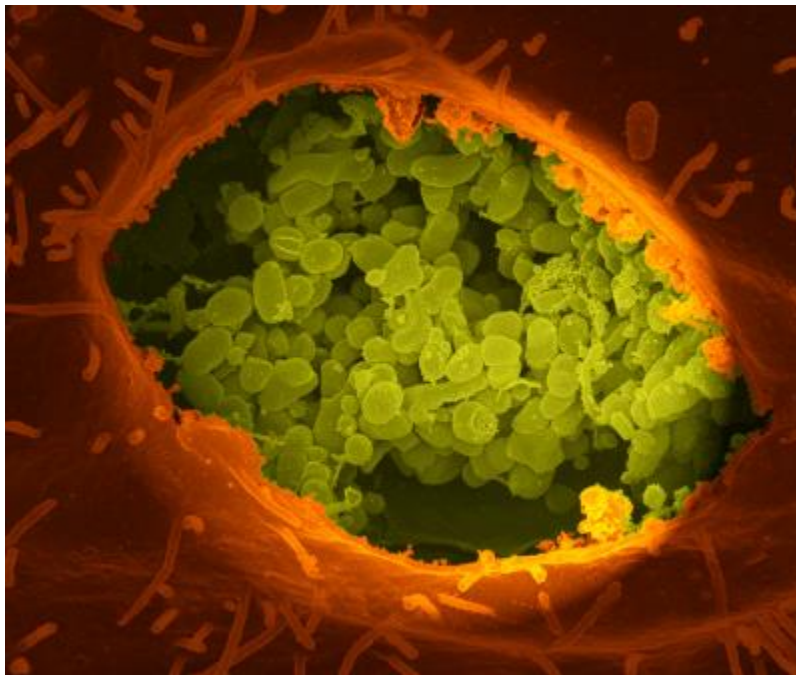
The other answers are trying to catch you out as fever, headache and rash are non specific symptoms. Artemether / lumefantrine is the correct treatment for uncomplicated *Plasmodium falciparum*; Benzylpenicillin is the treatment for Leptospirosis; Corticosteroid would be used to treat Katayama fever (acute schistosomiasis); and supportive care would be appropriate in the setting of uncomplicated dengue fever (typically an urban disease).

## Rickettsiae

Rickettsiae are Gram-negative obligate intracellular parasites. Types of rickettsiae cause a variety of diseases that are typically characterised by fever, headache and rash. A notable exception is Q fever (cause by *Coxiella burnetti* which causes pneumonia but no rash. The Weil-Felix reaction is positive except in Q fever. Rickettsial diseases are all treated with tetracyclines.

Disease	Cause	Vector	Notes
			Headache and fever are common
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	Tick	Rash starts on the peripheries (wrist, ankles) before spreading centrally. It is initially maculopapular before becoming vasculitic

Disease	Cause	Vector	Notes
			Endemic to east coast of US
Q fever	<i>Coxiella burnetii</i>	No vector	No rash but causes pneumonia
Endemic typhus	<i>Rickettsia typhi</i>	Flea	Rash starts centrally then spreads to the peripheries
Epidemic typhus	<i>Rickettsia prowazekii</i>	Human body louse	
Ehrlichiosis	<i>Ehrlichia</i>	Tick	



A dry fracture of a Vero cell exposing the contents of a vacuole where *Coxiella burnetii* are busy growing. Note the intracellular nature of the organism. Credit: NIAID

#### Question 5 of 56

A 35-year-old ex intravenous drug user has been diagnosed with has HBe-Ag positive Hepatitis B. Her investigation results are shown below:

HBV DNA 2100 IU/ml  
ALT 60 IU/L

ALT last checked 3 months ago and found to be ALT 60 IU/L.

What is the recommended first line treatment for this patient?

[Tenofovir disoproxil17%Entecavir17%Peginterferon alfa-2a51%Telbivudine8%Sofosbuvir7%](#)

The correct answer here is Peginterferon alfa-2a.

In patients who do not undergo HBeAg seroconversion or who relapse, tenofovir disoproxil is second line. Entecavir is an alternative second line when patients are unable to tolerate tenofovir disoproxil. Telbivudine is no longer recommended for the treatment of chronic Hepatitis B. Sofosbuvir is used for treating hepatitis C.

Please go to the link below for more information:

<https://www.nice.org.uk/guidance/CG165/chapter/1-Recommendations>

## **Hepatitis B**

Hepatitis B is a double-stranded DNA hepadnavirus and is spread through exposure to infected blood or body fluids, including vertical transmission from mother to child. The incubation period is 6-20 weeks.

The features of hepatitis B include fever, jaundice and elevated liver transaminases.

Complications of hepatitis B infection

- chronic hepatitis (5-10%)
- fulminant liver failure (1%)
- hepatocellular carcinoma
- glomerulonephritis
- polyarteritis nodosa
- cryoglobulinaemia

Immunisation against hepatitis B (please see the Greenbook link for more details)

- children born in the UK are now vaccinated as part of the routine immunisation schedule. This is given at 2, 3 and 4 months of age
- at risk groups who should be vaccinated include: healthcare workers, intravenous drug users, sex workers, close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, chronic liver disease patients



- contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology
- around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression
- testing for anti-HBs is only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease. In these patients anti-HBs levels should be checked 1-4 months after primary immunisation
- the table below shows how to interpret anti-HBs levels:

<b>Anti-HBs level (mIU/ml)</b>	<b>Response</b>
> 100	Indicates adequate response, no further testing required. Should still receive booster at 5 years
10 - 100	Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required
< 10	Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

#### Management of hepatitis B

- pegylated interferon-alpha used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy
- whilst NICE still advocate the use of pegylated interferon first-line other antiviral medications are increasingly used with an aim to suppress viral replication (not in a dissimilar way to treating HIV patients)
- examples include tenofovir and entecavir

#### Question 6 of 56

A 69-year-old man from Pakistan presents to his general practitioner with a three month history of cough associated with episodes of haemoptysis and has had some episodes of shortness of breath. His only past medical history of note is asthma for which he takes salbutamol inhaler as required and 2 puffs of beclomethasone inhaler twice daily. He has a 25 pack-year history and he is teetotal. The patient's GP performs blood tests and refers the patient to the rapid access chest clinic.

Blood test results come back as all within normal reference ranges, however, chest x-ray shows a solid lesion at the apex of the right lung, that is associated with a rim of air.

Of the following options, which is the most likely diagnosis?

[Tuberculosis18%](#)[Mesothelioma5%](#)[Aspergilloma65%](#)[Squamous cell carcinoma7%](#)[Small cell lung carcinoma5%](#)

The most likely diagnosis in this case is an aspergilloma - a fungal ball located in a previous cavity in the lung, as seen by the solid mass coupled with the rim of air and the haemoptysis, which can sometimes be severe.

## **Aspergilloma**

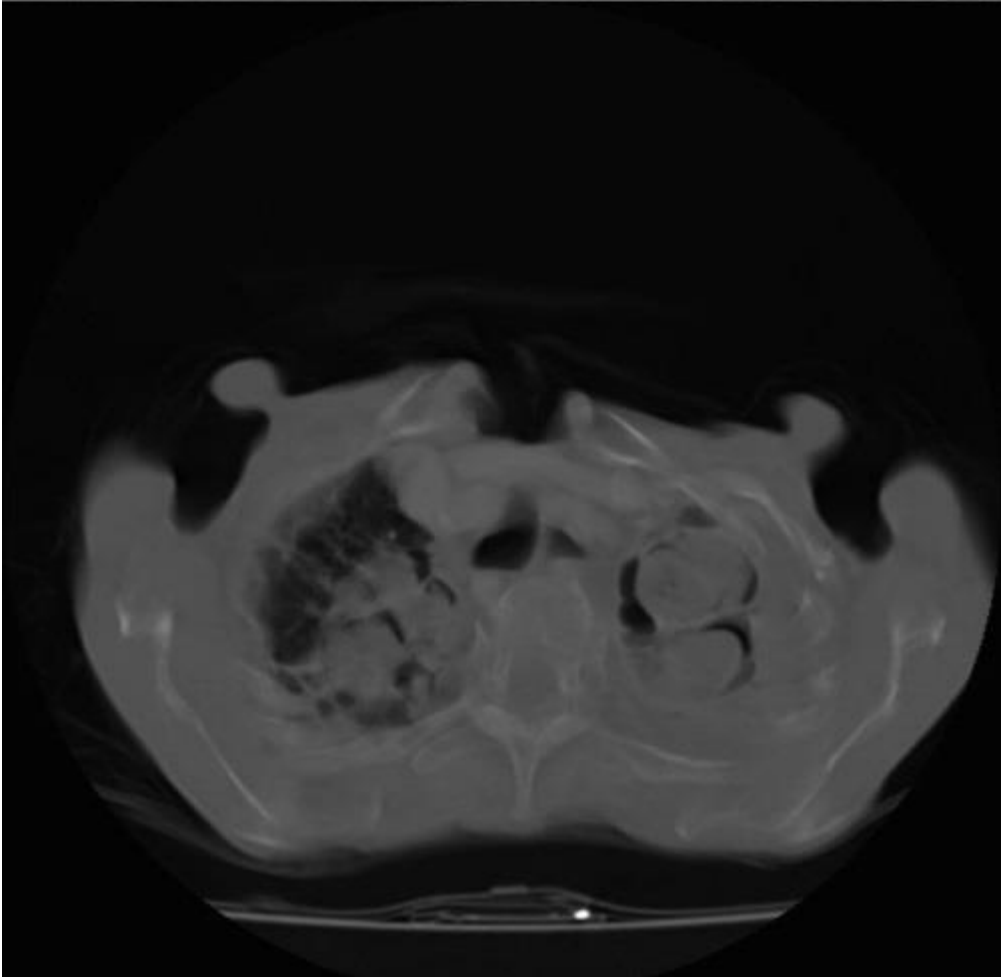
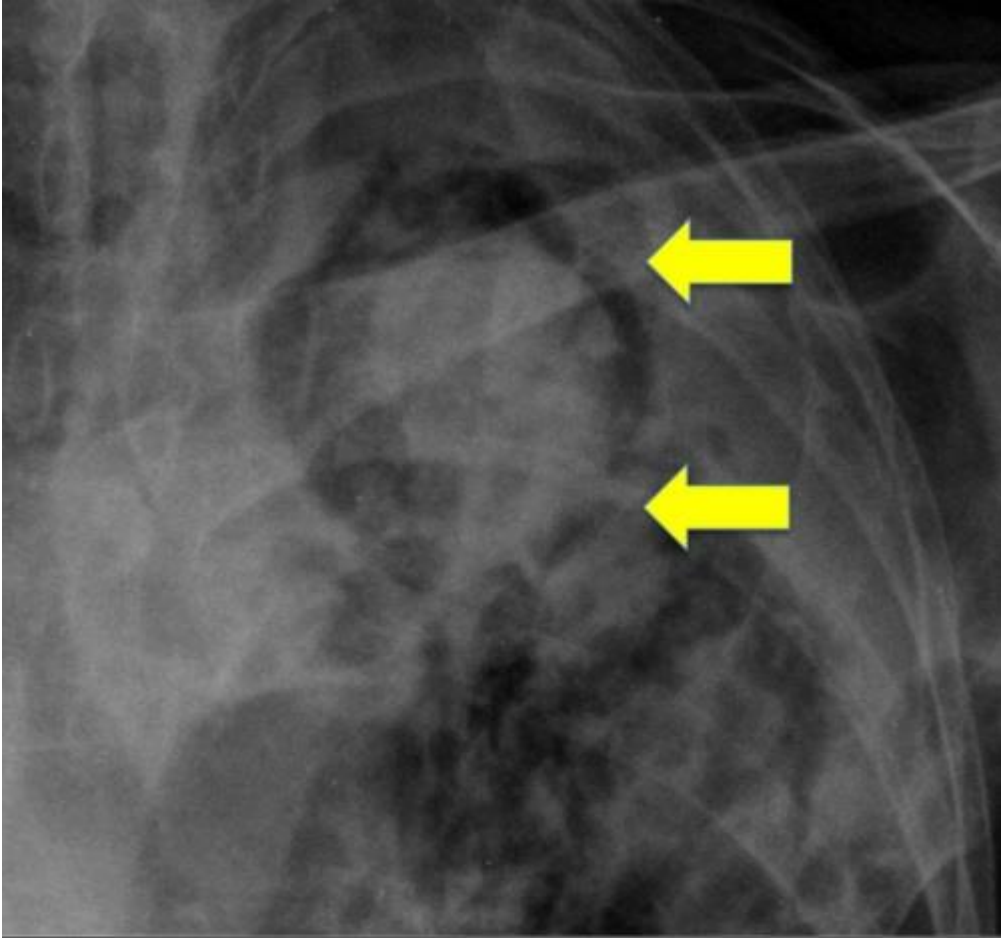
An aspergilloma is a mycetoma (mass-like fungus ball) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer or cystic fibrosis)

Usually asymptomatic but features may include

- cough
- haemoptysis (may be severe)

## **Investigations**

- chest x-ray containing a rounded opacity
- high titres Aspergillus precipitins





Aspergilloma in a patient with cavities secondary to previous tuberculosis infection. The close-up CXR and CT scan from the same patient demonstrate a rounded soft tissue attenuating masses located in a surrounding cavity.

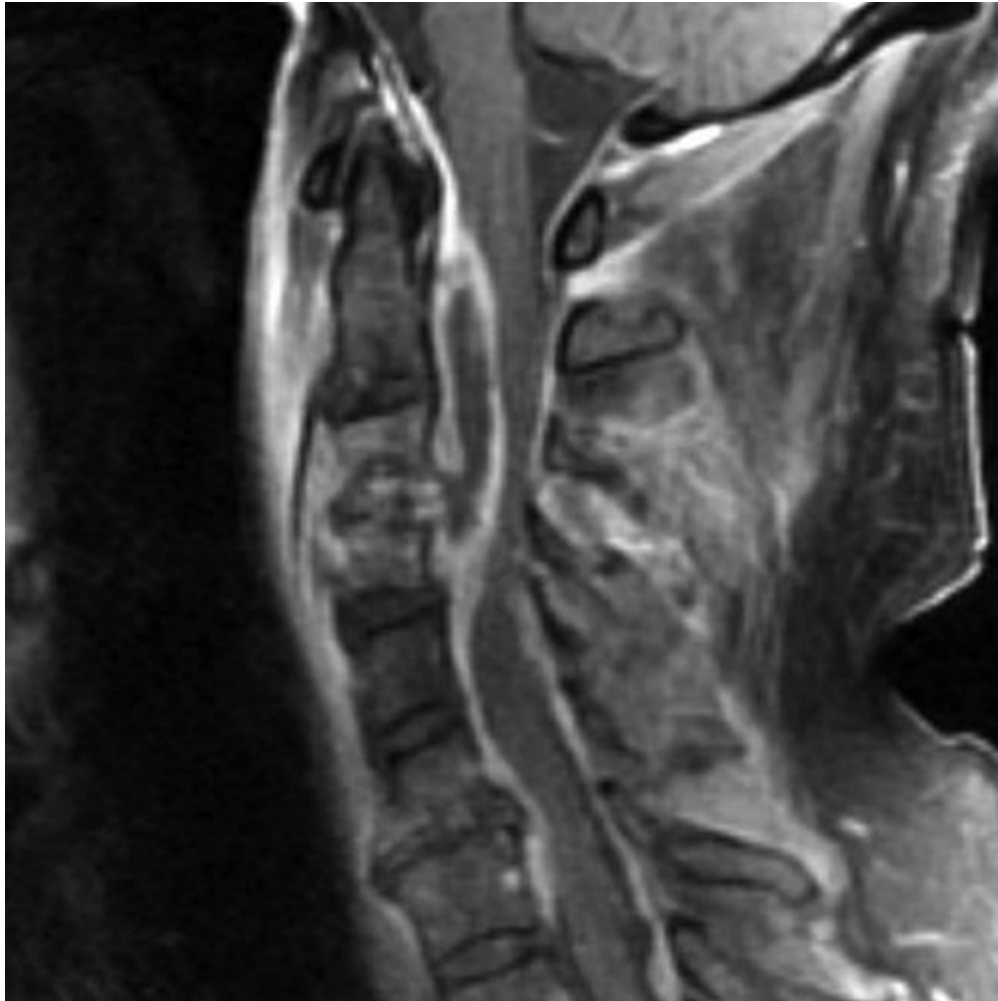
#### Question 1 of 50

A 54-year-old man presents with neck pain and feeling generally unwell. This has been getting progressively worse over the past two weeks and is now 'unbearable'. He feels hot and also complains of headaches.

He emigrated from Pakistan 30 years ago. He smokes 20 cigarettes/day and does not drink alcohol.

On examination pulse is 102/min, blood pressure 124/74 mmHg and temperature 37.9°C. He has weakness in both arms

MRI of his cervical spine is shown below:



© Image used on license from [Radiopaedia](#)



What is the most likely diagnosis?

[Cervical disc prolapse6%](#)[Syringomyelia10%](#)[Cervical epidural abscess47%](#)[Meningitis4%](#)[Tuberculosis34%](#)

MRI demonstrates an epidural collection with peripheral contrast enhancement. The cord is displaced posteriorly and to the right. Features are consistent with an epidural abscess. There are associated changes at the C3/4 level consistent with advanced discitis osteomyelitis.

## Spinal epidural abscess

Key features include

- spinal pain
- fever
- neurological deficit

#### Question 2 of 50

A 23-year-old man attends the emergency department after arriving back in the UK from a one-year trip travelling in South America. He denies any acute medical problems but reports that he is concerned about a dog bite he had received in Brazil about three months previously. The patient had been on a rain-forest expedition when a dog from the village he was staying in became aggressive and bit him on the left hand, leaving a open wound. The local inhabitants of the village had then chased the dog away. The patient had received first aid from his tour guide and been provided with a course of oral antibiotics. The wound had then healed over the following two weeks. It was only when the patient had been speaking with fellow travellers shortly before he returned to the UK did he realise the possible risk for rabies exposure.

The patient was well in himself and denied any neurological or other symptoms. He had no significant past medical history and took no regular medications. He admitted that he had not adequately researched his travel health needs before leaving the UK and so had not had any vaccinations prior to his trip.

Examination of the patients wound demonstrated fully healed scars consistent with a bite marks across the palm and dorsal surface of the wrist. The limb had normal neurological and vascular examination and the patient reported normal function of the hand.

What is the correct statement regarding rabies post-exposure prophylaxis for this patient?

The patient should receive rabies vaccination but not rabies immunoglobulin as his wound has now healed24% The patient does not require post-exposure prophylaxis as he remains free of symptoms following the incubation period of rabies18% The patient should receive rabies immunoglobulin and full rabies vaccination schedule46% The patient does not require rabies post-exposure prophylaxis as he did not receive his injury in a high-risk region4% The patient should receive rabies immunoglobulin but not rabies vaccination as this is only of benefit if given pre-exposure7%

The patient requires immediate (if belated) rabies post-exposure prophylaxis. Penetrating wounds are considered high risk-exposures, especially those to highly innervated areas such as the hands. The history of an unprovoked animal biting is also of concern.

Rabies immunoglobulin should be given no matter how long has elapsed since the exposure. As much as possible of the immunoglobulin dose should be infiltrated around the wound, with the remainder given as an IM gluteal injection. This should be combined with a full course of rabies vaccination (typically a 5-dose schedule with doses at day 0, 3, 7, 14 and 28). Such post-exposure prophylaxis is highly effective in preventing the rabies virus reaching the nervous

system.

Large parts of South America and Central America (including Brazil) are considered high-risk rabies regions. The virus is also endemic in Africa, the Middle East, Eastern Europe and most of Asia.

The incubation period of rabies can be prolonged and the patient is certainly still at risk of contracting the disease. One study found a mean incubation time of 274 days (range 12 days to 10 years).

Crowcroft N, Thampi N. The prevention and management of rabies. BMJ 2015;350:g7827.

<http://www.who.int/rabies/human/adminimmuno/en/>

## **Rabies**

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus (specifically a lyssavirus) and has a bullet-shaped capsid. The vast majority of cases are caused by dog bites but it may also be transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Rabies is estimated to still kill around 25,000-50,000 people across the world each year. The vast majority of the disease burden falls on people in poor rural areas of Africa and Asia. Children are particularly at risk.

### **Features**

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at-risk countries:

- the wound should be washed
- if an individual is already immunised then 2 further doses of vaccine should be given

- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination. If possible, the dose should be administered locally around the wound

If untreated the disease is nearly always fatal.

#### Question 3 of 50

A 41-year-old man is admitted to the Emergency Department after having a seizure. He has no history of epilepsy but is known to be HIV positive. On examination he is still slightly confused post-ictally but there are no focal neurological signs. He is afebrile and haemodynamically stable.

His current medications include efavirenz, tenofovir, lamivudine and co-trimoxazole.

His latest CD4 count is 38 cells/ $\mu$ l.

CT scan (without contrast) is shown below:



What is the most likely diagnosis?



[Cerebral toxoplasmosis 6%](#)[Progressive multifocal leukoencephalopathy 6%](#)[Cryptococcal infection 6%](#)[CNS lymphoma 76%](#)[Cerebral tuberculosis 5%](#)

A hyper-attenuating mass adjacent to the left lateral ventricle is seen. The homogenous appearance, position and history (low CD4 count and current use of co-trimoxazole prophylaxis) are suggestive of primary CNS lymphoma rather than cerebral toxoplasmosis.

## **HIV: neurocomplications**

### **Focal neurological lesions**

#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



© Image used on license from [Radiopaedia](#)



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
Thallium SPECT negative	Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 4 of 50

A 25-year-old man reports feeling unwell with fever, generalised muscle aches, headache and widespread rash 1 week after returning from Thailand. On admission his chest X-ray is unremarkable. His urine dip showed 1+ protein only and viral swabs are negative. Bloods are also normal aside from low platelet count. On day 2 of admission his blood pressure drops and repeat bloods show a further fall in platelets and reduction in haemoglobin count. What is the most likely diagnosis?

[Measles 6%](#) [Malaria 11%](#) [Dengue fever 72%](#) [Gonococcal septicaemia 6%](#) [Herpes simplex encephalitis 4%](#)

All plausible options and further history including prior vaccination, sexual history and malaria prophylaxis would be helpful. The history and deterioration are most likely due to dengue fever and subsequent 'dengue shock syndrome'. Measles would be unlikely at his age, malaria does not classically cause a widespread rash and herpes simplex would not cause a drop in the platelets. Gonorrhoea fits quite well and has a similar incubation period (4-7 days) . The patient would have normally have reported an isolated septic joint by this stage in the disease.

## **Dengue fever**

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

### Basics

- transmitted by the Aedes aegypti mosquito
- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

### Features

- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

### Question 2 of 45

A 22-year-old man presented to his General Practitioner with an itchy rash across his arms and legs. Symptoms had developed within the last few days and were causing the patient significant discomfort and preventing him from sleeping. The patient was a university student currently enjoying his summer vacation. He reported returning from a backpacking trip around Eastern

Europe one week previously when he had stayed mostly in youth hostels. Since his return he had been staying in his parent's home. Interestingly, the patient had discovered on Facebook that a similar rash had afflicted a friend he had made at the end of his holiday.

He also worked part-time as a barman and denied coming into contact with any unusual chemicals at work. He had not recently introduced any new skin care products.

The patient had suffered from mild atopic eczema as an infant but had no recent skin complaints or other past medical history. He took no regular medications and had no known allergies. The patient smoked 10 cigarettes per day and drank roughly 40 units of alcohol each week.

On examination, the patient's arms and legs were covered with 2-5 mm maculopapular lesions with a central haemorrhagic punctum. In several places, several lesions were noted to be lying close together in a curve formation. There were minor marks of excoriation associated with the lesions. The patient's groin, abdomen, chest and back were free from rash. There was no axillary, cervical or inguinal lymphadenopathy.

What organism is the likely cause for the patient's rash?

[Sarcoptes scabiei](#)45%[Leishmania donovani](#)12%[Ancylostoma braziliense](#)9%[Mycobacterium leprae](#)5%[Cimex hemipterus](#)30%

The patient has symptoms and signs of exposure to bed bug infestation. In temperate regions this is caused by the insect *Cimex hemipteru* (or *Cimex lectularius* in tropical regions). A rash develops up to 11 days after exposure due to an allergic reaction. Bed bug infestation has increased in frequency over the past 10 years with the patient likely exposed during a recent stay at youth hostel.

The other organisms are all potential causes of skin disease in the returned traveller.

- *Sarcoptes scabiei* (scabies)
- *Leishmania donovani* (cutaneous leishmaniasis)
- *Ancylostoma braziliense* (cutaneous larva migrans)
- *Mycobacterium leprae*(leprosy)

Bernardeschi C, Le Cleach L, Delaunay P. Bed bug infestation. BMJ 2013;346:f138.

## **Bed bugs**

Bed bugs describes a variety of clinical problems including skin rashes, bites and allergic

symptoms secondary to infestation with *Cimex hemipteru*.

They are controlled by hot-washing bed linen and using mattress covers.

#### Question 1 of 45

A 33-year-old male with a previous history of asthma and HIV presents for review to HIV clinic. He has been noticing weight gain, marks on his abdomen and his partner has noticed that his face has been looking more heavy-set over the last two months. He was diagnosed as having HIV at the age of 19 following needle sharing and use of heroin. He has had good retroviral control following starting treatment at the age of 20 with tenofovir, emtricitabine, atazanavir and ritonavir. His asthma has been well controlled with only salbutamol until six months ago when due to recurrent exacerbation due to upper respiratory tract infection his treatment was escalated to include regular fluticasone. Repeat blood tests show an undetectable viral load and a CD4 count of 900 cells/microliter. What is the most likely cause of his symptoms?

[Weight gain secondary to tenofovir use15%](#) [Weight gain secondary to emtricitabine use11%](#) [Weight gain due to reduced exercise tolerance4%](#) [Endogenous Cushing's syndrome8%](#) [Iatrogenic Cushing's syndrome62%](#)

The correct answer is iatrogenic Cushing's syndrome. HIV protease inhibitors are potent P450 inhibitors. This means that there are many possible interactions that should be checked before starting treatment. In this gentleman, hepatic enzyme inhibition has resulted in increased steroid dose from his regular inhaler for his asthma. This also explains the physical description showing standard Cushingoid features. Endogenous Cushing's syndrome is possible but is less likely, and weight gain from other causes would not explain all the physical changes described.

Source:

Saberi, Parya, Tony Phengrasamy, and Dong Phuong Nguyen. Inhaled Corticosteroid Use in HIV-Positive Individuals Taking Protease Inhibitors: A Review of Pharmacokinetics, Case Reports, and Clinical Management. *HIV medicine* 14.9 (2013): 519529. PMC. Web. 7 Mar. 2017.

### **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as



soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

#### Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

#### Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

#### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

#### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

#### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

#### Question 3 of 45

A 29-year-old woman who is a former intravenous drug user is seen in the hepatology clinic. She is 12 weeks pregnant and has been referred as she is known to have chronic hepatitis C. Twelve months ago she was treated with pegylated interferon-alpha, ribavirin and a protease inhibitor which failed to result in her clearing the hepatitis C virus.

What is the most appropriate way, if any, to reduce the risk of vertical transmission?

Caesarean section 28% Further course of antiviral therapy during pregnancy 8% Advise against breastfeeding 12% Antiviral therapy for the neonate for the first 4 weeks 15% None of the above interventions is recommended 37%

## **Hepatitis C and pregnancy**

Hepatitis C is likely to become a significant public health problem in the UK in the next decade. It is thought around 200,000 people are chronically infected with the virus. At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

Women in the UK are not currently screen for hepatitis C in the antenatal period.

### **Transmission risk**

- the vertical transmission rate from mother to child is about 6%. The risk is higher if there is a high viral load or coexistent HIV

### **Management**

- there are no definitive guidelines for the management of women with hepatitis C in pregnancy, the following is based on expert reviews
- standard drug therapy cannot be used in pregnancy due to concerns about teratogenicity
- the evidence base surrounding the use of caesarean section vs vaginal delivery is inconclusive, but it is not currently routine practice to offer a caesarean section. Cochrane state: *'Currently there is no evidence from randomised controlled trials upon which to base any practice recommendations regarding planned caesarean section versus vaginal delivery for preventing mother to infant Hepatitis C Virus transmission'*
- exposure to maternal blood e.g. due to perineal tears significantly increases the risk of passing on the virus
- breastfeeding is not contraindicated in mothers with hepatitis C

#### Question 4 of 45

A 65-year-old man is referred to gastroenterology clinic for advice prior to planned overseas travel. The patient states that he is planning to visit relatives in Brazil in two months time and is very concerned about the possibility of contracting travellers' diarrhoea in light of his previous and current medical history.

The patient had undergone a total colectomy with ileostomy formation twenty years previously, as curative treatment for severe ulcerative colitis. He had subsequently learnt to manage his ileostomy well and had declined reconstructive surgery. Ten years previously, the patient had contracted diarrhoea while travelling in the Caribbean, which he reported had ruined his holiday and complicated his ileostomy management for weeks.

Of more pressing concern was a recent diagnosis of small-cell lung cancer, for which the patient was undergoing chemotherapy with cisplatin and etoposide. The patient's chemotherapy regime was due to be completed four weeks before his proposed travel.

Aside from the issues outlined above, the patient's only other past medical history included hypertension for which he took ramipril. The patient denied any drug allergies or intolerances.

Standard precautions regarding the avoidance of travellers' diarrhoea were discussed with the patient, who fully acknowledged the risks of travelling so soon after completing chemotherapy.

What is appropriate management to help prevent travellers' diarrhoea in this patient?

[Vibrio cholerae vaccination10%Standard advice regarding hygiene precautions only41%Co-amoxiclav prophylaxis while overseas5%Ciprofloxacin prophylaxis while overseas36%Low-dose loperamide7%](#)

Travellers' diarrhoea is most commonly caused by *Escherichia coli* species and *Campylobacter jejuni*. Less common causative pathogens include *Salmonella* and *Shigella* species, parasitic infections such as *Giardia lamblia*, and viruses such as norovirus.

In the majority of individuals, diarrhoea is annoying and unpleasant but does not lead to long-term sequelae. However, some groups of individuals may be unable to tolerate the consequences of dehydration from diarrhoea, or be vulnerable to invasive complications such as bacteraemia.

The patient presented in this question will be immunosuppressed secondary to his chemotherapy and has an under-lying bowel condition due to his ileostomy. Therefore, he should be considered for antibiotic prophylaxis to prevent travellers' diarrhoea, following discussion of the risks of antibiotic associated diarrhoea and other side effects. When antibiotic prophylaxis is used, typical choices of agent are ciprofloxacin, norfloxacin or rifaximin.

Anti-motility agents such as loperamide can be helpful in limiting diarrhoea in individuals unable to tolerate dehydration, but does not have a role in preventing infection. Symptoms of invasive colitis, such as severe abdominal pain or bloody diarrhoea, are contra-indications to the

use of anti-motility agents due to the risk of intestinal perforation. Vaccination against cholera is effective, however is not a common cause of travellers' diarrhoea.

Barrett J, Brown M. Travellers' diarrhoea. BMJ 2016;353:i1937.

## Gastroenteritis

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The most common cause is *Escherichia coli*

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

## Stereotypical histories

Infection	Typical presentation
<i>Escherichia coli</i>	Common amongst travellers Watery stools Abdominal cramps and nausea
<b>Giardiasis</b>	Prolonged, non-bloody diarrhoea
<b>Cholera</b>	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers
<i>Shigella</i>	Bloody diarrhoea Vomiting and abdominal pain
<i>Staphylococcus aureus</i>	Severe vomiting Short incubation period
<i>Campylobacter</i>	A flu-like prodrome is usually followed by crampy abdominal pains, fever and diarrhoea which may be bloody  Complications include Guillain-Barre syndrome Two types of illness are seen
<i>Bacillus cereus</i>	<ul style="list-style-type: none"><li>• vomiting within 6 hours, stereotypically due to rice</li><li>• diarrhoeal illness occurring after 6 hours</li></ul>

Infection	Typical presentation
Amoebiasis	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks

Incubation period

- 1-6 hrs: *Staphylococcus aureus*, *Bacillus cereus*\*
- 12-48 hrs: *Salmonella*, *Escherichia coli*
- 48-72 hrs: *Shigella*, *Campylobacter*
- > 7 days: Giardiasis, Amoebiasis

\*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

Question 1 of 41

A previously well 28-year-old man presents with shortness of breath and abdominal discomfort. He reports a dry cough for the previous 10 days. He works full time as a management consultant. He is a non-smoker and drinks approximately 20 units of alcohol a week. He went on a stag-do to Prague with a bunch of friends 2 weeks ago. In the last few days, he has noticed a widespread skin rash which he describes as lots of pink rings around a pale centre.

Bloods on admission:

Na<sup>+</sup> 128 mmol/l  
 K<sup>+</sup> 3.7 mmol/l  
 Urea 8.2 mmol/l  
 Creatinine 150 µmol/l

Chest x-ray: Diffuse reticular infiltrates and small right-sided pleural effusion.

What is the most likely causative organism?

[\*Staphylococcus aureus\*5%\*Pneumocystis jirovecii\*5%\*Mycoplasma pneumoniae\*79%\*Streptococcus pneumoniae\*6%\*Haemophilus influenzae\*5%](#)

This patient has community-acquired pneumonia. Whilst *Streptococcus pneumoniae* and *Haemophilus influenzae* are the commonest causative organisms they tend to present with a shorter history. The longer duration of symptoms and unusual features of abdominal pain, dry cough and hyponatraemia should alert you to an atypical organism of which *Mycoplasma pneumoniae* is one of the commonest. The patient also describes erythema multiforme which is seen with *Mycoplasma pneumoniae*.

*Mycoplasma pneumoniae* occurs in epidemics every three to four years and typically affects

younger people. It tends to have an insidious onset with flu-like symptoms and atypical features. Hyponatraemia is often seen. Cold agglutinins can cause an autoimmune haemolytic anaemia. Diagnosis is confirmed with Mycoplasma serology. Treatment is with clarithromycin or a tetracycline or fluoroquinolone.

Staphylococcal pneumonia may complicate influenza infection and is seen most frequently in the elderly and in intravenous drug users or patients with underlying disease. It can result in a cavitating pneumonia.

*Pneumocystis jirovecii* is seen in immunocompromised patients. It typically presents with exertional breathlessness and patients are seen to desaturate on walking. Whilst a HIV test should be considered in the diagnostic workup of this patient, it is not the most likely diagnosis in this case.

### ***Mycoplasma pneumoniae***

*Mycoplasma pneumoniae* is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

#### Features

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

#### Complications

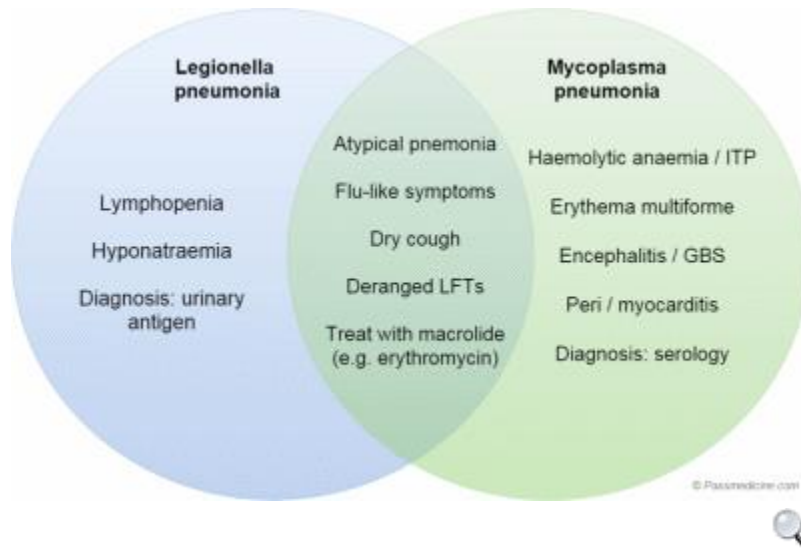
- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

#### Investigations

- diagnosis is generally by Mycoplasma serology
- positive cold agglutination test

## Management

- erythromycin/clarithromycin
- tetracyclines such as doxycycline are an alternative



## Comparison of Legionella and Mycoplasma pneumonia

### Question 1 of 40

A 30-year-old man returns from a stag do in Amsterdam with fever, headache and abdominal pain. He was away for 2 days and drunk 40-50 units of alcohol. He also had unprotected sex with a local girl and vaguely remembers falling in the canal on the second night. He is febrile with a blood pressure 100/70 mmHg. His bloods tests reveal :

Routine tests in the emergency department are ordered:

Hb 95 g/l WBC  $20 \times 10^9/l$  , Platelets  $150 \times 10^9/l$

$Na^+$  135 mmol/l ,  $K^+$  5.0 mmol/l

Urea 15 mmol/l , Creatinine 300  $\mu$ mol/l

Bilirubin 35  $\mu$ mol/l , ALP 200 u/l , ALT 70 u/l

CXR - pulmonary haemorrhage

What is the most likely diagnosis?

[Acute hepatitis A5%](#) [Acute hepatitis B5%](#) [Goodpastures syndrome16%](#) [Leptospirosis68%](#) [Atypical pneumonia6%](#)

This gentleman should be screened for viral hepatitis and have an HIV test, however given the results of his investigations infection with *Leptospira* from falling in the contaminated water is the most likely diagnosis. The acuity and neutrophilia go against Goodpasture's syndrome and an atypical pneumonia would not classically cause pulmonary haemorrhage.

## Leptospirosis

Also known as Weil's disease\*, leptospirosis is commonly seen in questions referring to sewage workers, farmers, vets or people who work in abattoir. It is caused by the spirochaete *Leptospira interrogans* (serogroup L icterohaemorrhagiae), classically being spread by contact with infected rat urine. Weil's disease should always be considered in high-risk patients with hepatorenal failure

### Features

- fever
- flu-like symptoms
- renal failure (seen in 50% of patients)
- jaundice
- subconjunctival haemorrhage
- headache, may herald the onset of meningitis

### Management

- high-dose benzylpenicillin or doxycycline

\*the term Weil's disease is sometimes reserved for the most severe 10% of cases that are associated with jaundice

### Question 2 of 40

A 52-year-old woman presents to the emergency department with a swollen, hot and painful leg. This has worsened over 24 hours but was the same as her other leg before. She has a past



medical history of bilateral leg lymphoedema which is normally managed with compression bandaging. She also has hypertension, atrial fibrillations and mitral stenosis. She takes amlodipine, apixaban and bisoprolol. She is normally mobile with walking aids, limited by the oedema. On examination, she has a swollen left leg which has an area of blanching erythema, roughly 25x10 cm which is hot and tender on touch. Both legs also show evidence for chronic swelling with oedema. She has a temperature of 37.9°C as well, but her observations are otherwise normal. A doppler US of her leg is normal. What is the most appropriate management strategy?

[IV benzylpenicillin and flucloxacillin 42% Oral flucloxacillin 44% Oral clindamycin 7% Subcutaneous dalteparin 4% IV meropenem 4%](#)

In lymphoedema, management of cellulitis should be with IV rather than oral antibiotics even when patient not systemically unwell

This is a patient with cellulitis as is demonstrated by the unilateral hot, tender, erythematous and swollen with an elevated temperature and negative Doppler study. Normally, this patient could be managed on oral antibiotics as the patient is systemically well does not have decompensated systemic illness, but since she has significant lymphoedema IV antibiotics are needed. The BNF advises IV benzylpenicillin and flucloxacillin for cellulitis. Oral flucloxacillin would be correct if the patient was for oral antibiotics, and oral clindamycin could be considered if she was not responding to oral flucloxacillin.

## Cellulitis

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by *Streptococcus pyogenes* or *Staphylococcus aureus*.

### Features

- commonly occurs on the shins
- erythema, pain, swelling
- there may be some associated systemic upset such as fever

### Criteria for admission

NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis:

#### Class

#### Features

I There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities

<b>Class</b>	<b>Features</b>
II	The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection
III	The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromise
IV	The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis

They recommend the following that we admit for intravenous antibiotics the following patients:

- Has Eron Class III or Class IV cellulitis.
- Has severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
- Is very young (under 1 year of age) or frail.
- Is immunocompromised.
- Has significant lymphoedema.
- Has facial cellulitis (unless very mild) or periorbital cellulitis.

The following is recommend regarding Eron Class II cellulitis:

*Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person - check local guidelines.*

Other patients can be treated with oral antibiotics.

## **Management**

The BNF recommends flucloxacillin as first-line treatment for mild/moderate cellulitis. Clarithromycin or clindamycin is recommend in patients allergic to penicillin.

Many local protocols now suggest the use of oral clindamycin in patients who have failed to respond to flucloxacillin.

Severe cellulitis should be treated with intravenous benzylpenicillin + flucloxacillin.



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#### Question 4 of 40

A 19-year-old man presents to the Sexual Health clinic for a routine check-up.

He is homosexual and describes having unprotected sex with a number of partners over the last 3 months. He has no regular partner currently.

He reports he has been generally well apart from a bad cold he had 6 weeks ago. He undergoes an HIV test which is positive.

Further investigations reveal:

CD4 count  $0.67 \times 10^9/L$  ( $0.3 \times 10^9/L$  -  $1.4 \times 10^9/L$ )

CD8 count  $1.35 \times 10^9/L$  ( $0.5 \times 10^9/L$  -  $10 \times 10^9/L$ )

Viral load 24,378 RNA/mL ( $<20 \text{ RNA/mL}$ )

What is the correct management of this patient?

6 monthly monitoring. Start antiretroviral therapy when CD4 count is  $<0.35 \times 10^9/L$  5% Start antiretroviral therapy as soon as suitable patient counselling can occur 84% Monitor 3 monthly. If viral load increases to  $<100,000 \text{ RNA/mL}$ , start antiretroviral therapy 4% Monitor patient. Advise

him he does not need to start antiretroviral therapy currently as long as he uses barrier contraception in all his future sexual encounters 4% 6 monthly monitoring. Start antiretroviral therapy when CD4 count is  $<0.35 \times 10^9/L$  and patient has a major infection 4%

The 2015 BHIVA guidelines advised that all patients diagnosed with HIV should start an antiretroviral therapy no matter what their CD4 count, viral load or state of their health at that time, therefore answer 1,2,4 and 5 are all wrong as they all choose not to start antiretroviral therapy as soon as possible.

<http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf>

This man should also be advised to practice safe sex with all his partners no matter what his HIV status is or whether he is on anti-retroviral therapy or not. He will also receive regular monitor to ensure he is coming to terms with his diagnosis and that his CD4 count and viral load improve or remain satisfactory.

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

### Question 1 of 35

A 38-year-old man is admitted to the Emergency Department with shortness-of-breath and a non-productive cough. He has recently emigrated from Russia and has just started anti-retroviral therapy for HIV.

Examination of his chest is unremarkable. His temperature is 37.7°C and oxygen saturations are 95% on room air.

A chest x-ray is performed:



© Image used on license from [Radiopaedia](#)



What is the most likely diagnosis?

[Cytomegalovirus 8%](#) [Mediastinal lymphoma 4%](#) [Tuberculosis 11%](#) [Mycoplasma pneumoniae 7%](#) [Pneumocystis jiroveci pneumonia 70%](#)

The key to answering this question is to look at the history rather than the x-ray. A combination of HIV + chest symptoms + unremarkable auscultatory findings in an exam are highly suggestive of *Pneumocystis jiroveci* pneumonia (more commonly known as PCP). X-ray changes in *Pneumocystis jiroveci* pneumonia are generally too subtle for non-radiologists to detect. The x-ray should however help you to exclude some of the other diagnoses.

The chest x-ray shows hazy, perihilar mid and upper zone opacification with some interstitial prominence. A few discrete cysts (termed pneumatocoeles) measuring up to 1cm are present. The presence of pneumatocoeles in a HIV patient suggests *Pneumocystis jiroveci* pneumonia.

**HIV: *Pneumocystis jiroveci* pneumonia**

Whilst the organism *Pneumocystis carinii* is now referred to as *Pneumocystis jiroveci*, the term *Pneumocystis carinii* pneumonia (PCP) is still in common use

- *Pneumocystis jiroveci* is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count  $< 200/\text{mm}^3$  should receive PCP prophylaxis

### Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

### Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

### Management

- co-trimoxazole
- IV pentamidine in severe cases
- steroids if hypoxic (if  $\text{pO}_2 < 9.3\text{kPa}$  then steroids reduce risk of respiratory failure by 50% and death by a third)



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

#### Question 2 of 35

A 17-year-old man is referred to the infectious disease department with a sore throat, fever and lymphadenopathy. He has been generally unwell for the previous 3 days but presented as he noticed some yellowing of his eyes. His routine blood test show-

Bilirubin 55  $\mu\text{mol/l}$

ALP 54 u/l

ALT 402 u/l

AST 188 u/l

$\gamma\text{GT}$  17 u/l

Albumin 43 g/l

He has no travel or sexual history and has never used intravenous drugs. What is the most likely causative organism?



[Viridans group Streptococci6% Hepatitis B virus6% Echinococcus granulosus6% Hepatitis C virus5% Epstein Barr virus \(EBV\)77%](#)

Epstein-Barr virus (EBV) is a herpes virus which commonly leads to infectious mononucleosis. This presents, often in teenagers and young adults with fevers, painful throat, lymphadenopathy and flu-like symptoms. Although it can last longer the symptoms are usually self-limiting within 2 weeks. Acute infection often leads to splenomegaly or hepatosplenomegaly and although a transient hepatitis is common it can lead to clinical jaundice.

### **Infectious mononucleosis**

Infectious mononucleosis (glandular fever) is caused by the Epstein-Barr virus (EBV, also known as human herpesvirus 4, HHV-4) in 90% of cases. Less frequent causes include cytomegalovirus and HHV-6. It is most common in adolescents and young adults.

The classic triad of sore throat, pyrexia and lymphadenopathy is seen in around 98% of patients:

- sore throat
- lymphadenopathy: may be present in the anterior and posterior triangles of the neck, in contrast to tonsillitis which typically only results in the upper anterior cervical chain being enlarged
- pyrexia

Other features include:

- malaise, anorexia, headache
- palatal petechiae
- splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- hepatitis, transient rise in ALT
- lymphocytosis: presence of 50% lymphocytes with at least 10% atypical lymphocytes
- haemolytic anaemia secondary to cold agglutins (IgM)
- a maculopapular, pruritic rash develops in around 99% of patients who take ampicillin/amoxicillin whilst they have infectious mononucleosis

Symptoms typically resolve after 2-4 weeks.

Diagnosis

- heterophil antibody test (Monospot test) - NICE guidelines suggest FBC and Monospot in the 2nd week of the illness to confirm a diagnosis of glandular fever.

Management is supportive and includes:

- rest during the early stages, drink plenty of fluid, avoid alcohol
- simple analgesia for any aches or pains
- consensus guidance in the UK is to avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture

There is an interesting correlation between EBV and socioeconomic groups. Lower socioeconomic groups have high rates of EBV seropositivity, having frequently acquired EBV in early childhood when the primary infection is often subclinical. However, higher socioeconomic groups show a higher incidence of infectious mononucleosis, as acquiring EBV in adolescence or early adulthood results in symptomatic disease.

#### Question 3 of 35

An elderly gentleman presents with a three day history of bloody diarrhoea and feverishness. He has no significant travel history. His past medical history is listed as hypertension, osteoarthritis and gout. On examination his temperature is 38.0°C, heart rate 95/min, blood pressure 120/80 mmHg and his abdomen is soft and non-tender. A stool sample has grown *Salmonella*. What is the best treatment?

[Metronidazole11%Doxycycline8%Clarithromycin7%Ciprofloxacin70%Amoxicillin4%](#)

The BNF recommends treating invasive diarrhoea (causing bloody diarrhoea and fever) with ciprofloxacin. Most viral or bacterial gastroenteritis do not require treatment. The BNF recommends antibiotics for bacterial gastroenteritis in severe infections or in immunocompromised patients. Clarithromycin is used for traveller's diarrhoea and non-invasive diarrhoeal illnesses when treatment is necessary.

## Gastroenteritis

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one or more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The most common cause is *Escherichia coli*

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin. Acute food poisoning is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*.

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<i>Campylobacter</i>	A flu-like prodrome is usually followed by crampy abdominal pains, fever and diarrhoea which may be bloody  Complications include Guillain-Barre syndrome Two types of illness are seen
<i>Bacillus cereus</i>	<ul style="list-style-type: none"> <li>• vomiting within 6 hours, stereotypically due to rice</li> <li>• diarrhoeal illness occurring after 6 hours</li> </ul>
<b>Amoebiasis</b>	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks

### Incubation period

- 1-6 hrs: *Staphylococcus aureus*, *Bacillus cereus*\*
- 12-48 hrs: *Salmonella*, *Escherichia coli*
- 48-72 hrs: *Shigella*, *Campylobacter*
- > 7 days: Giardiasis, Amoebiasis

\*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

A 48-year-old farmer presents with a four-day history of headache, pyrexia and vomiting. He has recently been undergoing chemotherapy for mantle cell lymphoma and successfully completed his fourth cycle three days ago. During his treatment, he has tried to maintain an active lifestyle and has continued to work on his dairy farm. He has no other past medical history, he does not smoke or drink. On examination, the patient is drowsy and pyrexia at 38.6 degrees. You note no rashes on his skin. He displays neck stiffness and photophobia. You are unable to formally perform a neurological examination but you note no obvious facial asymmetry and the patient is moving all four limbs. Both plantars are downgoing.

Blood tests are as follows:

Hb 98 g/l  
Platelets  $78 \times 10^9/l$   
WBC  $0.9 \times 10^9/l$   
Neutrophils  $0.3 \times 10^9/l$

Na<sup>+</sup> 146 mmol/l  
K<sup>+</sup> 4.3 mmol/l  
Urea 8 mmol/l  
Creatinine 99  $\mu$ mol/l  
CRP 170 mg/l

A lumbar puncture is performed and the cerebrospinal fluid examination is as follows:

WCC  $200 \times 10^6/litre$  (70% neutrophil 25% lymphocytes)  
RBC  $4 \times 10^6/litre$   
Glucose 1.7 mmol/l (normal 3.3-4.4 mmol/l)  
Microscopy No organisms on gram stain  
Appearance cloudy

The patient is immediately commenced on intravenous ceftriaxone for suspected bacterial meningitis. At 48 hours after initial admission, blood and cerebrospinal fluid cultures are still awaited. The patient has demonstrated no change in clinical state. What is an appropriate additional therapy?

[Hourly neurological monitoring4%](#)[Intravenous acyclovir16%](#)[Intravenous ampicillin32%](#)[Intravenous rifampicin14%](#)[Intravenous amphotericin B34%](#)

A diagnosis of meningitis is clear. However, the context is that of a patient who is immunocompromised with recent chemotherapy, presenting with a relatively subacute cause of neutropenic sepsis. The additional information that he continues to work on a dairy with possible exposure to unpasteurised milk increases the chance of listeria exposure, for which intravenous ampicillin is the most appropriate treatment. The patient has demonstrated no improvement in 48

hours; antibiotic escalation would be appropriate. It should be noted that on CSF examination, the absence of an organism on Gram staining does not equate to the absence of an organism! Only one-third of listeria meningitis patients are likely to grow an organism on Gram stain. In addition, listeria meningitis is a classic example of bacterial meningitis when a significant proportion of lymphocytes may be in CSF (>25%), instead of predominant neutrophilia. These include TB, rickettsial and cryptococcal meningitis. With no mention of previous or active TB exposure and no pulmonary symptoms on a relatively short history, TB meningitis is only a low-risk possibility. Intravenous amphotericin B would be appropriate for fungal meningitis only.

## Listeria

*Listeria monocytogenes* is a Gram positive bacillus which has the unusual ability to multiply at low temperatures. It is typically spread via contaminated food, typically unpasteurised dairy products. Infection is particularly dangerous to the unborn child where it can lead to miscarriage.

Features - can present in a variety of ways

- diarrhoea, flu-like illness
- pneumonia , meningoencephalitis
- ataxia and seizures

Suspected Listeria infection should be investigated by taking blood cultures. CSF may reveal a pleocytosis, with 'tumbling motility' on wet mounts

## Management

- Listeria is sensitive to amoxicillin/ampicillin (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

## In pregnant women

- pregnant women are almost 20 times more likely to develop listeriosis compared with the rest of the population due to changes in the immune system
- fetal/neonatal infection can occur both transplacentally and vertically during child birth
- complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- treatment is with amoxicillin

### Question 5 of 35

A 19-year-old man returned from a year long gap year project in West Africa. He finished in Gabon and noticed swelling in his right arm. Since returning to the United Kingdom he has had intermittent swelling of his right forearm for the last 6 weeks. This is not localised to a joint, moves around and is non tender - lasting a few days before disappearing again. What is the most likely diagnosis?

[Fleeting inflammatory arthritis9%Loa-Loa47%Mastocytosis10%Cutaneous leishmaniasis24%Sweet syndrome10%](#)

Loa-Loa is one of three nematodes (roundworm) that cause cutaneous filariasis. Cases are very rare in the UK these days but the disease can still be seen in returning travellers.

The life cycle includes the parasite *Loa loa*, the fly vector, and the human host. *Loa loa* parasites local inflammation along the subcutaneous tracks that they travel called Calabar swellings. These usually only last 1-3 days but an immunological response weeks later may cause a localised angioedema. *Loa loa* can also invade eyes and other systemic symptoms include itching, joint pain and fatigue.

The two other filariae causing disease are *Mansonella streptocerca* and *Onchocerca volvulus*. Onchocerciasis causes river blindness and remains a huge public health problem in central and west Africa. In 1974 a control programme was launched which has been very successful - initially through larvicide spraying of fast-flowing rivers to control black fly populations and then subsequently treating at risk population groups empirically with ivermectin.

## Loiasis

Loiasis is a filarial infection caused by *Loa Loa*. It is transmitted by the *Chrysops* deerfly and tends to occur in rainforest regions of Western and Central Africa.

### Clinical features

- pruritus
- urticaria
- Calabar swellings: transient, non-erythematous, hot swelling of soft-tissue around joints
- 'eye worm' - the dramatic presentation of subconjunctival migration of the adult worm.

It has less pathological features than other the microfilarial infections *Onchocerciasis* and

Lymphatic Filariasis. However high loa loa microfilaraemia is associated with encephalopathy following treatment with either Ivermectin or DEC. This occurs due to the death of vast numbers of blood microfilaria. Both of these drugs are contraindicated if loa loa microfilaraemia exceeds 2500 mf/ml.

This has significant public health implications as Ivermectin is currently the drug of choice for control of both Onchocerciasis and Lymphatic Filariasis in Africa.



Adult Loa loa parasite. Loa loa is the filarial nematode (roundworm) species that causes loa loa filariasis. It is commonly known as the 'eye worm.' Its geographic distribution includes Africa and India. Credit: NIAID

#### Question 7 of 35

A 27 year old Caucasian man has just returned from a 12 week trip to Ivory Coast where he was working as a missionary. He had not consulted a travel clinic for immunisations and had taken no malaria prophylaxis. During his trip he slept in a hammock outside and he took a daily wash in the river near the church where he was working. For the last few days of his trip he felt very unwell. He developed fevers, muscle aches and a headache, however this was improving and he had been feeling much better when he arrived home in the UK.

He has been home for 24 hours. Today he felt very much worse and presented to A and E.

On admission:

- Temperature: 39.1C
- Blood pressure: 89/61mmHg
- Pulse: 68 / min
- Respiratory rate: 26 / min
- Oxygen saturations: 97% on room air.

His initial investigations show:

Hb 11.1 g/dl  
Platelets  $61 \times 10^9/l$   
WBC  $3.3 \times 10^9/l$   
Neutrophils  $2.6 \times 10^9/l$   
Lymphocytes  $0.6 \times 10^9/l$

Na<sup>+</sup> 146 mmol/l  
K<sup>+</sup> 4.1 mmol/l  
Bicarbonate 16 mmol/l  
Urea 17.4 mmol/l  
Creatinine 321 mol/l

Bilirubin 88 mol/l  
ALP 322 u/l  
ALT 821 u/l  
 $\gamma$ GT 421 u/l  
Albumin 29 g/l

Following discussion with the ID consultant on call, he is isolated while a blood sample is sent to Public Health England's imported fever service. He received empirical therapy for Malaria with Artesunate and for sepsis with Piperacillin/Tazobactam and Gentamicin, however he rapidly deteriorated and died within 24 hours of admission. Following discussion with Public Health England, who confirm that there was no evidence of a nosocomially transmitted Viral Haemorrhagic Fever, he has a post mortem examination which reveals Councilman bodies in his liver.

What would likely have prevented his death?

[Sleeping under an insecticide treated bed net 13%](#)  
[Avoiding bathing in the river 24%](#)  
[Live attenuated Yellow Fever vaccine 46%](#)  
[Prophylaxis with doxycycline 11%](#)  
[Avoiding unprotected sex 5%](#)

This is yellow fever as suggested by:

- Travel to endemic area ( West Africa and Central America )
- Fever, with initial resolution
- Progression to jaundice and renal failure



For exam purposes Councilman bodies (eosinophilic inclusion in the liver on post mortem) are diagnostic of yellow fever, although they can occasionally be seen in other Viral Haemorrhagic Fevers such as Crimean Congo Haemorrhagic Fever, (but this is nosocomially spread and therefore not the case in this example).

As such the vaccination is the only intervention which could have prevented his death.

## **Yellow fever**

Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

### Basics

- spread by *Aedes* mosquitos
- incubation period = 2 - 14 days

### Features

- may cause mild flu-like illness lasting less than one week
- classic description involves sudden onset of high fever, rigors, nausea & vomiting. Bradycardia may develop. A brief remission is followed by jaundice, haematemesis, oliguria
- if severe jaundice, haematemesis may occur
- Councilman bodies (inclusion bodies) may be seen in the hepatocytes

### Question 6 of 35

A 54 year old Caucasian man with HIV, is stable on Tenofovir, Emtricitabine and Kaletra (Lopinavir/Ritonavir). He has a 60 pack year smoking history and has been told his blood pressure is high previously but had never previously been to see his GP about it to get it treated. His GP is unaware of his HIV diagnosis and his main point of healthcare contact is with the Genito-urinary medicine services.

However over the last two years he has been troubled by gradually worsening cough, and shortness of breath. He has not lost weight. This has spurred him to start seeing his GP. He says that his GP initially gave him a blue inhaler and did some tests and told him he had COPD. Six

weeks ago his GP gave him a Seretide 500 inhaler (one puff twice a day) and started him on Rampril (2.5mg daily) for his high blood pressure. The purple inhaler had provided some relief to his breathlessness but four days ago it ran out and he hasn't yet been back to see his GP. He still has two weeks worth of Ramipril tablets.

For the last few days he has been feeling faint and dizzy especially when standing up. His breathlessness and cough are no worse than usual. He has no fever. On examination his blood pressure is 91/76 his pulse is 94. He is afebrile, his respiratory rate is 24 and his oxygen saturations are 92% on room air. He has a mild wheeze on auscultation of his chest. His heart sounds are faint and his JVP is visible 3cm above his sternal angle. There is no pitting oedema. There is nothing else of note on examination.

An ECG on admission is normal.

Hb 14.0 g/dl  
Platelets  $199 \times 10^9/l$   
WBC  $6.2 \times 10^9/l$

Na<sup>+</sup> 130 mmol/l  
K<sup>+</sup> 5.9 mmol/l  
Urea 5.6 mmol/l  
Creatinine 85  $\mu$ mol/l  
CRP 7 mg/l

What is the diagnosis?

[Adrenal tuberculosis 25%](#)[Pericardial tuberculosis 12%](#)[Adrenal insufficiency secondary to inhaled corticosteroid withdrawal 37%](#)[Ramipril induced hypotension 10%](#)[Waterhouse-Friderichsen syndrome 17%](#)

A very difficult question. The timing of events is key.

Fluticasone in Seretide is metabolised by P450 and Ritonvir inhibits this allowing very high levels of systemic steroid with consequent adrenal insufficiency. Cessation of Seretide has caused this Addisonian event (low sodium, high potassium is the clue).

Disseminated TB would be unusual with no fever or weight loss but is an important differential, especially in the context of HIV infection. All of his findings on examination are consistent with COPD.

Waterhouse-Friderichsen syndrome is bilateral adrenal haemorrhage in the context of meningococcal septicaemia.

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

## Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

### Question 1 of 25

A 60-year-old man presented with history of excessive urination especially during night which disturbs his sleep, excessive thirst and tiredness for the past 2 months. He was a known HIV positive patient for which he was on highly active anti-retroviral therapy (HAART) since 6 months. Clinical examination was within normal limits. HIV related diabetes mellitus was suspected by the treating physician. His blood investigations are as follows-

Hb	150 g/l
Platelets	$150 \times 10^9/l$
WBC	$7 \times 10^9/l$
Fasting blood glucose	10 mmol/l
Post prandial blood glucose	13.9 mmol/l
Serum creatinine	130 $\mu\text{mol/L}$

He was planned to be started on metformin therapy. Which of the following investigations is important to be checked before starting metformin in this patient?.

[Liver enzymes22%](#) [Venous lactate61%](#) [Serum triglycerides7%](#) [Serum albumin4%](#) [Serum ammonia6%](#)

Patients with HIV are at increased risk of lactic acidosis and hence it is prudent to check lactate levels before starting metformin in such patients. Lactic acidemia with no or mild symptoms was detected in 8% to 21% of patients receiving at least 1 nucleoside reverse transcriptase inhibitor, versus 0% to 1% of patients receiving no antiretroviral therapy. Symptomatic lactic acidemia is less common (occurring in about 1.5% 2.5%). Monitoring for lactic acidosis is recommended in the initial few months of metformin therapy. Patients with impaired renal function (serum creatinine >1.5 mg/dl) or with a venous lactate level more than twice the normal level prior to treatment should not be started on metformin.

This patient has an elevated serum creatinine but not >1.5mg/dl. So, he should get a venous lactate estimation before being started on metformin therapy considering the evidences so far.

### Reference:

- 1) Clinical medicine 2014 Vol 14, No 6: 667-9
- 2) <http://www.intmedpress.com/serveFile.cfm?sUID=f0b9cf79-9ed3-41da-b1b5-57a2bbae687a>
- 3) <http://journals.lww.com/jaids/Abstract/2002/11010/ManagementofMetabolicComplicationsAss>

ociated.1.aspx (Management of Metabolic Complications Associated With Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS SocietyUSA Panel)

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Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition

- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

#### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

#### Question 2 of 25

A 31 year-old accountant was referred to the general medical clinic with persistent nasal stuffiness and intermittent epistaxis. He had been seen by the ear, nose and throat team who had commenced him on a course of intranasal steroids without benefit. His past medical history was unremarkable. His travel history included a gap year in South America 10 years previously. He was a non-smoker and drank 23 units of alcohol per week.

On examination, his temperature was 36.2°C, heart rate 68 beats per minute, respiratory rate 16 breaths per minute, blood pressure 126/82 mmHg. There was some superficial ulceration of the nasal mucosa bilaterally. The chest was clear on auscultation and heart sounds were normal.

#### Investigations:

Haemoglobin	145 g/L
White cell count	$7.0 \times 10^9/l$
Neutrophil count	$4.0 \times 10^9/l$
Lymphocyte count	$3.0 \times 10^9/l$
Eosinophil count	$0.4 \times 10^9/l$
Platelets	$300 \times 10^9/l$

Sodium	144 mmol/L
Potassium	4.1 mmol/L
Urea	6.1 mmol/L
Creatinine	71 mol/L
Alkaline phosphatase	56 IU/L
Alanine aminotransferase	35 IU/L
Gamma-glutyl transferase	21 IU/L
Bilirubin	13 mol/L
Albumin	39 g/L
Fasting plasma glucose	5.3 mmol/L

What is the most likely causative organism?

[Trypanosoma cruzi](#)15%[Plasmodium ovale](#)6%[Leishmania braziliensis](#)53%[Leishmania donovani](#)19%[Chlamydia trachomatis](#)8%

The most likely diagnosis in this case is mucosal leishmaniasis. The patient probably became infected with cutaneous leishmaniasis during his visit to South America, and received no/incomplete treatment. Mucosal leishmaniasis can occur years to decades after initial infection; typical features include nasal stuffiness and epistaxis in the early stages, progressing to ulceration and destruction of the nasal mucosa. *Leishmania donovani* is a recognised cause of visceral rather than mucocutaneous leishmaniasis.

## Leishmaniasis

Leishmaniasis is caused by the intracellular protozoa *Leishmania*, usually being spread by sand flies. Cutaneous, mucocutaneous leishmaniasis and visceral forms are seen

### Cutaneous leishmaniasis

- caused by *Leishmania tropica* or *Leishmania mexicana*
- crusted lesion at site of bite
- may be underlying ulcer

### Mucocutaneous leishmaniasis

- caused by *Leishmania braziliensis*
- skin lesions may spread to involve mucosae of nose, pharynx etc

### Visceral leishmaniasis (kala-azar)

- mostly caused by *Leishmania donovani*
- occurs in the Mediterranean, Asia, South America, Africa
- fever, sweats, rigors
- massive splenomegaly. hepatomegaly
- poor appetite\*, weight loss
- grey skin - 'kala-azar' means black sickness
- pancytopenia secondary to hypersplenism

\*occasionally patients may report increased appetite with paradoxical weight loss

Question 3 of 25

A 72-year-old man presents with a chronic cough. This has been getting gradually worse for the past 3 months. On around five occasions he has coughed up some blood stained sputum. His past medical history includes ischaemic heart disease (NSTEMI 4 years ago), spinal stenosis and tuberculosis (treated 50 years ago). He drinks 20 units of alcohol per week and has a 55 pack-year history of smoking.

On examination scattered crackles are noted in both lung fields, but are more prominent on the left.

A chest x-ray is requested:



© Image used on license from [Radiopaedia](https://radiopaedia.org/)





What is the most likely underlying diagnosis?

[Aspergilloma52%Reactivated tuberculosis18%Lung cancer13%Histoplasmosis9%Lung abscess8%](#)

The chest x-ray shows a cavity (secondary to old tuberculosis) in the left upper zone containing an aspergilloma. Please see below for an annotated close-up image with an accompanying CT scan from the same patient.

## **Aspergilloma**

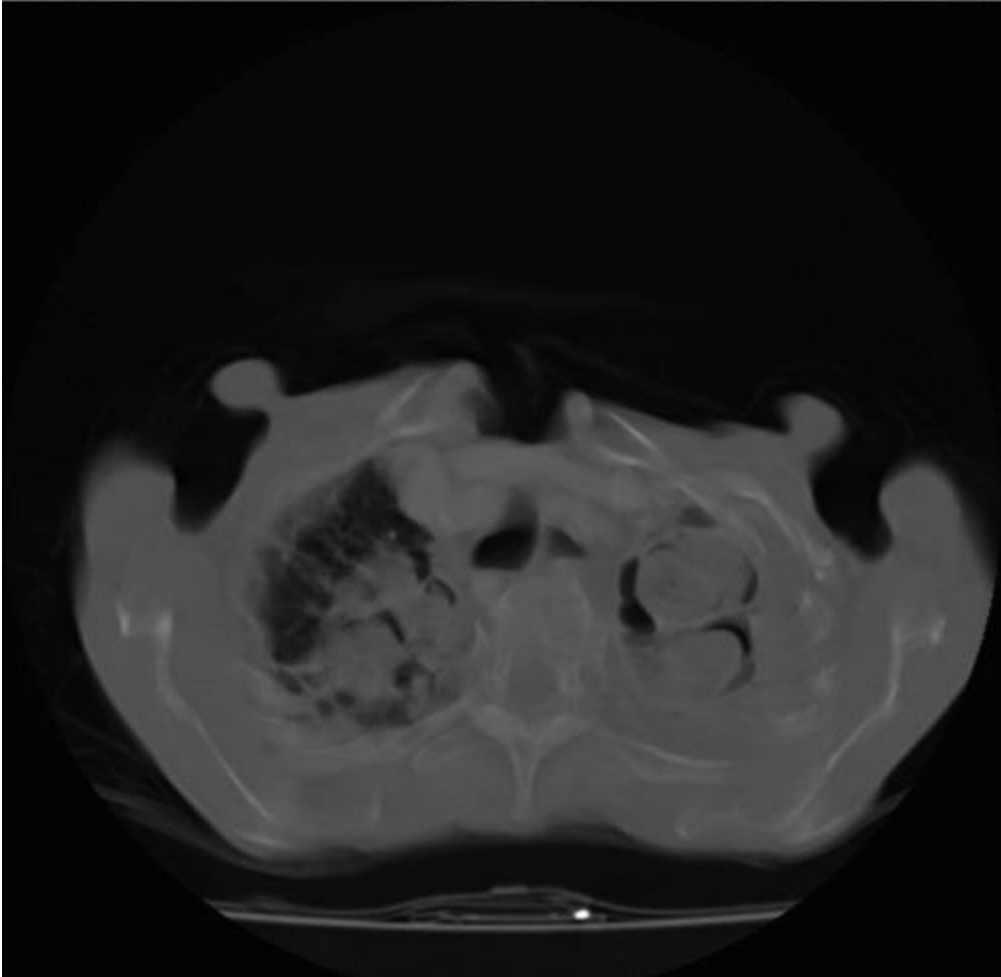
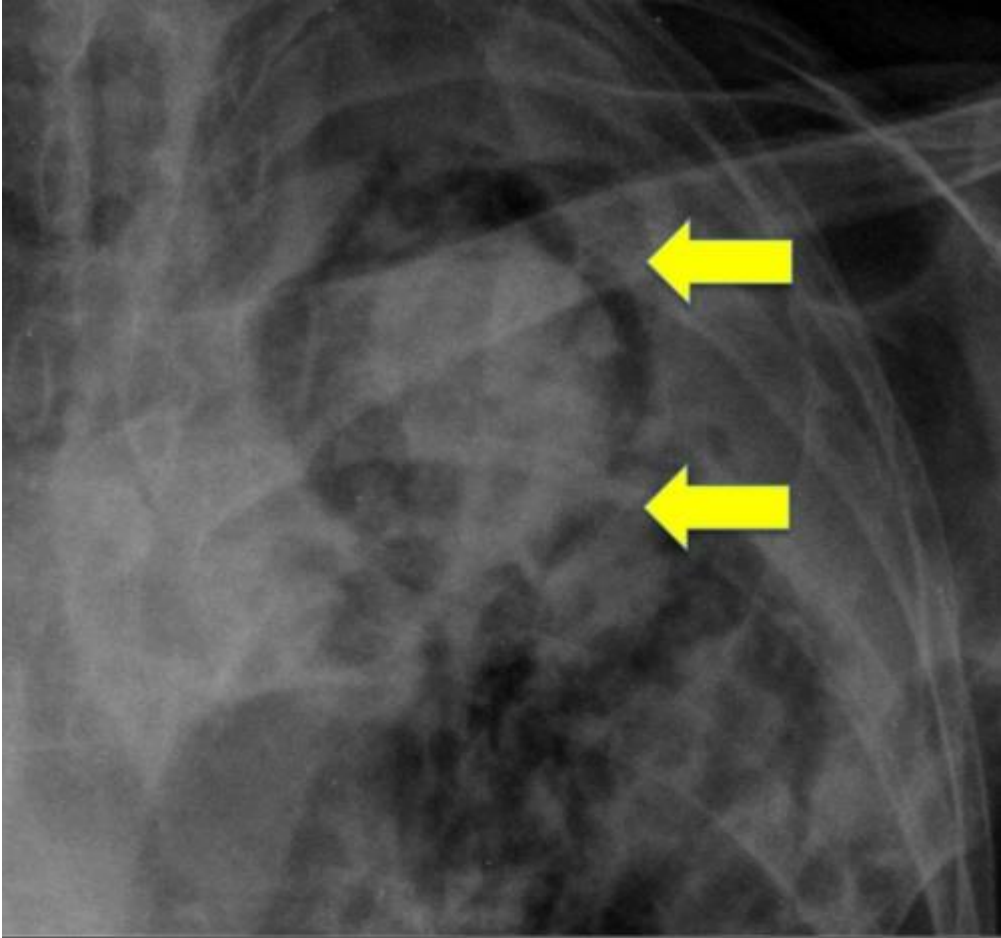
An aspergilloma is a mycetoma (mass-like fungus ball) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer or cystic fibrosis)

Usually asymptomatic but features may include

- cough
- haemoptysis (may be severe)

## **Investigations**

- chest x-ray containing a rounded opacity
- high titres Aspergillus precipitins





Aspergilloma in a patient with cavities secondary to previous tuberculosis infection. The close-up CXR and CT scan from the same patient demonstrate a rounded soft tissue attenuating masses located in a surrounding cavity.

#### Question 4 of 25

A 34-year-old man with chronic immune thrombocytopenia has not responded to medical therapy and so is scheduled to undergo an elective splenectomy. According to guidelines, he requires the following vaccinations:

[Pneumovax \(Pneumococcus\), Haemophilus Influenzae, MMR \(Measles, Mumps, Rubella\), Annual influenza vaccine](#)  
[7% Haemophilus Influenzae, Meningococcus C, Annual influenza vaccine](#)  
[6% Pneumovax \(Pneumococcus\), Haemophilus Influenzae, Meningococcus C, Annual influenza vaccine](#)  
[67% Pneumovax \(Pneumococcus\), Haemophilus Influenzae, Meningococcus C](#)  
[15% Meningococcus C, Haemophilus Influenzae, MMR \(Measles, Mumps, Rubella\), Annual influenza vaccine](#)  
[5%](#)

Risk of infection following splenectomy is with encapsulated bacteria e.g *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Neisseria meningitidis*. Therefore patients should be immunised against these infections. MMR vaccination is not required.

### Splenectomy

Following a splenectomy patients are particularly at risk from pneumococcus, Haemophilus, meningococcus and Capnocytophaga canimorsus\* infections

#### Vaccination

- if elective, should be done 2 weeks prior to operation
- Hib, meningitis A & C
- annual influenza vaccination
- pneumococcal vaccine every 5 years

#### Antibiotic prophylaxis

- penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be

continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

## **Surgical aspects**

### Indications

- Trauma: 1/4 are iatrogenic
- Spontaneous rupture: EBV
- Hypersplenism: hereditary spherocytosis or elliptocytosis etc
- Malignancy: lymphoma or leukaemia
- Splenic cysts, hydatid cysts, splenic abscesses

### Splenectomy following trauma

- GA
- Long midline incision
- If time permits insert a self retaining retractor (e.g. Balfour/ omnitract)
- Large amount of free blood is usually present. Pack all 4 quadrants of the abdomen. Allow the anaesthetist to 'catch up'
- Remove the packs and assess the viability of the spleen. Hilar injuries and extensive parenchymal lacerations will usually require splenectomy.
- Divide the short gastric vessels and ligate them.
- Clamp the splenic artery and vein. Two clamps on the patient side are better and allow for double ligation and serve as a safety net if your assistant does not release the clamp smoothly.
- Be careful not to damage the tail of the pancreas, if you do then this will need to be formally removed and the pancreatic duct closed.
- Wash out the abdomen and place a tube drain to the splenic bed.
- Some surgeons implant a portion of spleen into the omentum, whether you decide to do this is a matter of personal choice.
- Postoperatively the patient will require prophylactic penicillin V and pneumococcal vaccine.

### Elective splenectomy

- Elective splenectomy is a very different operation from that performed in the emergency setting. The spleen is often large (sometimes massive)
- Most cases can be performed laparoscopically. The spleen will often be macerated inside a specimen bag to facilitate extraction.

## Complications

- Haemorrhage (may be early and either from short gastrics or splenic hilar vessels)
- Pancreatic fistula (from iatrogenic damage to pancreatic tail)
- Thrombocytosis: prophylactic aspirin
- Encapsulated bacteria infection e.g. *Strep. pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*

## Post-splenectomy changes

- Platelets will rise first (therefore in ITP should be given after splenic artery clamped)
- Blood film will change over following weeks, Howell-Jolly bodies will appear
- Other blood film changes include target cells and Pappenheimer bodies
- Increased risk of post-splenectomy sepsis, therefore prophylactic antibiotics and pneumococcal vaccine should be given.

## Post-splenectomy sepsis

- Typically occurs with encapsulated organisms
- Opsonisation occurs but then not recognised

\*usually from dog bites

## Question 5 of 25

A 24 year old Somali woman attends her booking appointment in the UK for her first pregnancy. Screening tests reveal that she is HIV positive. She is asymptomatic.

Her viral load is 150 000 copies/ml and her CD4 count is 523 cells/mm<sup>3</sup>. No viral resistance is detected. Her hepatitis serology is negative. Her husband consequently tests negative for HIV.

She is commenced on triple anti-retroviral therapy (ART) with zidovudine, lamivudine and lopinavir/ritonavir. By 36 weeks her viral load is undetectable at <20 copies/ml.

Which of the following statements is true regarding her ongoing management?

She should have an elective caesarean section and continue to take her ART whilst breast-feeding. 9%  
She should have a vaginal delivery and continue to take ART whilst breast feeding. 14%  
She should have an elective caesarean section. ART should be continued. 22%  
She should have a vaginal delivery and formula feed. ART can be discontinued. 5%  
She should have a vaginal delivery and formula feed. ART should be continued. 50%

In this case, as her viral load is less than 50 copies/ml she may have a vaginal delivery. Formula feeding is recommended in the UK to all babies with HIV +ve mothers. In this case although her CD4 count is  $>350$  cells/mm<sup>3</sup> her ART should be continued to reduce the risk of onward transmission to her husband.

## **HIV and pregnancy**

With the increased incidence of HIV infection amongst the heterosexual population there are an increasing number of HIV positive women giving birth in the UK. In London the incidence may be as high as 0.4% of pregnant women. The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.

Guidelines regularly change on this subject and most recent guidelines can be found using the links provided.

Factors which reduce vertical transmission (from 25-30% to 2%)

- maternal antiretroviral therapy
- mode of delivery (caesarean section)
- neonatal antiretroviral therapy
- infant feeding (bottle feeding)

### **Screening**

- NICE guidelines recommend offering HIV screening to all pregnant women

### **Antiretroviral therapy**

- all pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously

### **Mode of delivery**

- vaginal delivery is recommended if viral load is less than 50 copies/ml at 36 weeks, otherwise caesarian section is recommended
- a zidovudine infusion should be started four hours before beginning the caesarean section

## Neonatal antiretroviral therapy

- zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used. Therapy should be continued for 4-6 weeks.

## Infant feeding

- in the UK all women should be advised not to breast feed

## Question 6 of 25

A 54-year-old oil businessman who frequently visits the Gambia and is usually careful with his malaria prophylaxis has been admitted with general malaise and relapsing/remitting fevers which seem to occur every third day. He returned from the Gambia about one week ago and on this occasion, he did not take his malaria prophylaxis as he has never caught it before. He has no past medical history of note and no regular medication. Malarial parasites are seen on the thick and thin films and it is confirmed as *Plasmodium vivax* by the Malaria Reference Laboratory.

What is the most appropriate management according to current UK guidelines?

[Chloroquine 13% Atovaquone-proguanil 10% Chloroquine and primaquine 47% Artemether with lumefantrine 17% Intravenous artesunate + primaquine 14%](#)

*Plasmodium vivax* is the second most commonly seen cause of malaria by UK statistics after *Plasmodium falciparum* malaria. It is characteristically a cause of benign tertian malaria where fevers occur every three days. Current UK guidelines (Health Protection Association) are that non-falciparum malaria should be treated with chloroquine but *P. vivax* and *P. ovale* are unusual in that dormant parasites (or hypnozoites) can exist within the liver.

The only currently available treatment for hypnozoites is primaquine and vivax malaria is more effectively treated with a higher dose than ovale (30mg). Therefore the correct answer is chloroquine and high-dose primaquine. Anyone commencing treatment with primaquine should have their glucose-6-phosphate dehydrogenase status tested as primaquine could precipitate severe haemolysis in deficient patients.

Artesunate, atovaquone-proguanil and artemether with lumefantrine are treatments for falciparum malaria.

## Malaria: non-falciparum

The most common cause of non-falciparum malaria is *Plasmodium vivax*, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases. *Plasmodium vivax* is often found in Central America and the Indian Subcontinent whilst *Plasmodium ovale* typically comes from Africa

### Features

- general features of malaria: fever, headache, splenomegaly
- *Plasmodium vivax/ovale*: cyclical fever every 48 hours. *Plasmodium malariae*: cyclical fever every 72 hours
- *Plasmodium malariae*: is associated with nephrotic syndrome

Ovale and vivax malaria have a hypnozoite stage and may therefore relapse following treatment.

### Treatment

- in areas which are known to be chloroquine-sensitive then WHO recommend either an artemisinin-based combination therapy (ACT) or chloroquine
- in areas which are known to be chloroquine-resistant an ACT should be used
- ACTs should be avoided in pregnant women
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse

### Question 7 of 25

A 24-year-old recent immigrant from Albania presents to the emergency department with fever, headache and malaise. Over the past 24 hours he has also developed bilateral pain and swelling at the angle of the jaw, which is made worse by talking or chewing. On examination his pulse is 90/min, temperature 38.4°C and bilateral palpable, tender parotid glands are noted.

Given the likely diagnosis, which one of the following complications is he most likely to develop?

[Orchitis67%Pancreatitis10%Encephalitis9%Myocarditis6%Pneumonia7%](#)

Orchitis is the most common complication of mumps in post-pubertal males.

There is a link between mumps and pancreatitis (the 'M' in GET SMASHED) but this is much less common than orchitis.



## Mumps

Mumps is caused by RNA paramyxovirus and tends to occur in winter and spring

### Spread

- by droplets
- respiratory tract epithelial cells → parotid glands → other tissues
- infective 7 days before and 9 days after parotid swelling starts
- incubation period = 14-21 days

### Clinical features

- fever
- malaise, muscular pain
- parotitis ('earache', 'pain on eating'): unilateral initially then becomes bilateral in 70%

### Prevention

- MMR vaccine: the efficacy is around 80%

### Management

- rest
- paracetamol for high fever/discomfort
- notifiable disease

### Complications

- orchitis - uncommon in pre-pubertal males but occurs in up to 50% of post-pubertal males
- hearing loss - usually unilateral and transient
- meningoencephalitis
- pancreatitis

A 54 year old intravenous drug user is newly diagnosed with HIV, after presenting with progressive shortness of breath. He was diagnosed with pneumocystis pneumonia and commenced on appropriate treatment.

His CD4 count is 54 cells/mm<sup>3</sup> and his viral load is  $1.7 \times 10^7$  copies per ml.

As part of his routine work up, it is also revealed that he has co-infection with Hepatitis C. A test for HIV viral tropism is reported as dual tropism virus.

Which drug is unlikely to be effective in this mans treatment?

[Maraviroc 30% Raltegravir 10% Tenofovir 19% Ribavirin 28% Abacavir 13%](#)

HIV virus binds to the CD4 cell via the CD4 receptor. This interaction also depend on viral interaction with the CD4 co-receptor. There are two forms of CD4 co-receptor CCR5 and CXCR4.

The test for viral tropism determines which of these co-receptors the HIV virus will bind to. Maraviroc blocks HIV binding to CCR5 receptor, and therefore is an effective drug in a 'CCR5 tropic' virus. It however is not effective if the virus is 'CXCR4 tropic' or 'dual tropic'. The tropism of the HIV virus will not effect the use of any of the other drugs listed.

It is routine to test HIV viral tropism on diagnosis, or on virological failure to assess if maraviroc is a therapeutic option.

## **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

### Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

### Question 9 of 25

A 42-year-old immigrant from Nigeria has been referred to the infectious disease clinic. He was feeling tired and generally unwell over several weeks since last visiting Nigeria, his country of origin. He has also travelled for business to the United States six months ago. He has had fever and rigors as well as headaches. Posterior lymph nodes have been present and have been aspirated one week ago, and trypomastigotes were present. What is the most likely causative organism?

[Trypanosoma rhodesiense](#)20% [Trypanosoma gambiense](#)50% [Trypanosoma cruzi](#)19% [Leishmania mexicana](#)5% [Leishmania tropica](#)6%

The correct answer is *Trypanosoma gambiense*. This is a patient with a clinical history suggestive of African trypanosomiasis with a slow wasting course. The presence of trypomastigotes means that there will be a *Trypanosoma* infection. The species can be

determined by geography. *Rhodesiense* occurs in east Africa whilst *gambiense* occurs in west Africa, including Nigeria. Uganda is the only country with both. *Cruzi* is endemic in South America and causes American trypanosomiasis. *Leishmania* are other protozoa occurring in Africa, South America and India.

## Trypanosomiasis

Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease)

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly. *Trypanosoma rhodesiense* tends to follow a more acute course. Clinical features include:

- Trypanosoma chancre - painless subcutaneous nodule at site of infection
- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis

### Management

- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract

- myocarditis may lead to dilated cardiomyopathy (with apical atrophy) and arrhythmias
- gastrointestinal features includes megaesophagus and megacolon causing dysphagia and constipation

### Management

- treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure

#### Question 10 of 25

A 28-year-old male presents to the emergency department complaining of shortness of breath. For the last week he has felt generally unwell with a headache, malaise and lethargy, but felt breathless this afternoon hence his presentation. On systems review, he also admits to having some generalised abdominal pain throughout the day yesterday associated with diarrhoea. He is otherwise fit and well, takes no regular medications and does not smoke. He admits to drinking one or two beers every evening and occasionally more at the weekends. He is a primary school teacher and lives with his wife and two small children, none of whom have been unwell recently. On examination, he has a temperature of 38.9°C, a heart rate of 105 beats/minute and a blood pressure of 105/70 mmHg. His respiratory rate is 26 breaths/minute, his oxygen saturations 92% breathing room air and on auscultation to his chest there are a few crepitations bibasally. He has some routine blood tests performed.

Hb 109 g/L  
 MCV 105 fL  
 Platelets  $390 \times 10^9/L$   
 WBC  $16.5 \times 10^9/L$   
 CRP 240 mg/L  
 Bilirubin 50  $\mu\text{mol/L}$   
 ALT 40 u/L  
 ALP 135 u/L

What is the most likely diagnosis?

[Alcoholic liver disease6%](#)[Gilbert's syndrome11%](#)[Mycoplasma pneumonia70%](#)[Hypothyroidism6%](#)[Acute cholecystitis7%](#)

Mycoplasma pneumonia is one of the atypical pneumonias and classically occurs in clusters every few years. It normally produces a fairly mild picture with fairly normal clinical findings although the chest x-ray may have marked changes. It is associated with cold agglutinins in around 50% of cases which can result in a cold autoimmune haemolytic anaemia - as in this case, explaining the slight bilirubin rise and the raised MCV which represents a reticulocytosis. Other associations with mycoplasma infection include erythema multiforme, encephalitis, arthralgia and diarrhoea. Alcoholic liver disease is possible given this patient's alcohol intake, bilirubin and MCV, but would be unlikely given his young age and no other clinical findings to support this. Gilbert's syndrome is hyperbilirubinaemia in the context of transient illness, viral or otherwise, and could explain many of the findings in this case but would not explain the raised MCV.

## ***Mycoplasma pneumoniae***

*Mycoplasma pneumoniae* is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of *Mycoplasma pneumoniae* classically occur every 4 years. It is important to recognise atypical pneumonias as they may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

### Features

- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

### Complications

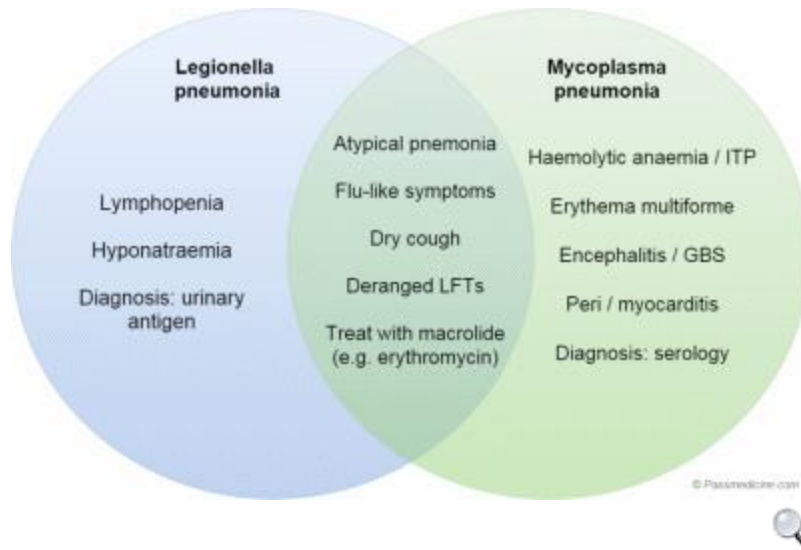
- cold agglutins (IgM) may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

### Investigations

- diagnosis is generally by *Mycoplasma* serology
- positive cold agglutination test

### Management

- erythromycin/clarithromycin
- tetracyclines such as doxycycline are an alternative



## Comparison of Legionella and Mycoplasma pneumonia

### Question 11 of 25

An 82-year-old gentleman inpatient is reviewed on the ward round. He originally presented with diarrhoea on a background of ulcerative colitis flare and is managed with oral and rectal mesalazine. His bowel has settled but he developed a rash around his left antecubital fossa, and he has developed a temperature of 38.2°C. On examination, his chest sounds clear and his abdomen is soft, but the left antecubital fossa has a tender and warm erythematous rash. Stool results show no growth, abdominal and chest X-ray are clear but a MRSA swab from the nose is positive. What is the most appropriate treatment?

[Mupirocin and chlorhexidine 27%](#) [Benzylpenicillin 4%](#) [Tazocin 4%](#) [Vancomycin 54%](#) [Flucloxacillin 10%](#)

The correct answer is vancomycin. This is a patient with a new fever and the most obvious cause is cellulitis. Given that the location of the cellulitis is in a location common for cannulation the most likely explanation is iatrogenic cellulitis. This makes MRSA a much higher likelihood and therefore the most appropriate treatment is vancomycin. Mupirocin and chlorhexidine are used to eradicate MRSA when present as commensal organisms. In non-iatrogenic cellulitis benzylpenicillin and flucloxacillin are commonly used.

## MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first organisms which

highlighted the dangers of hospital-acquired infections.

Who should be screened for MRSA?

- all patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded)
- from 2011 all emergency admissions will be screened

How should a patient be screened for MRSA?

- nasal swab and skin lesions or wounds
- the swab should be wiped around the inside rim of a patient's nose for 5 seconds
- the microbiology form must be labelled 'MRSA screen'

Suppression of MRSA from a carrier once identified

- nose: mupirocin 2% in white soft paraffin, tds for 5 days
- skin: chlorhexidine gluconate, od for 5 days. Apply all over but particularly to the axilla, groin and perineum

The following antibiotics are commonly used in the treatment of MRSA infections:

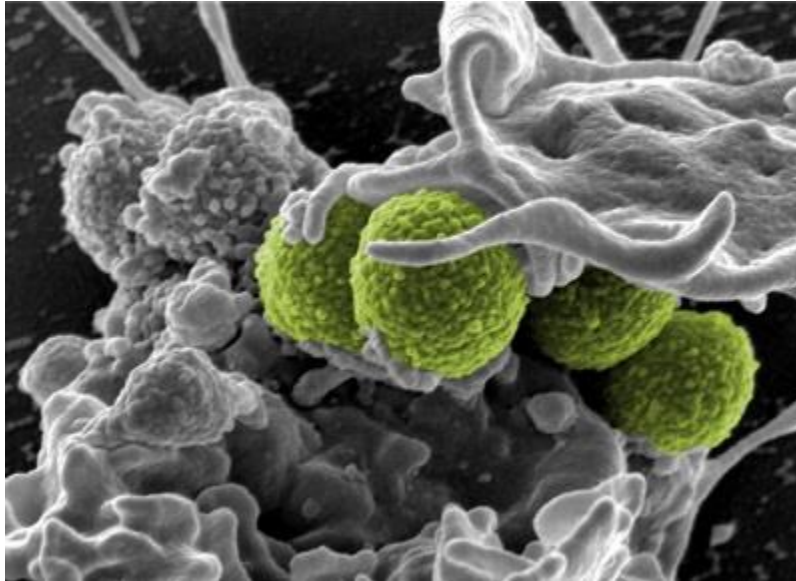
- vancomycin
- teicoplanin
- linezolid

Some strains may be sensitive to the antibiotics listed below but they should not generally be used alone because resistance may develop:

- rifampicin
- macrolides
- tetracyclines
- aminoglycosides
- clindamycin

Relatively new antibiotics such as linezolid, quinupristin/dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases





Interaction of MRSA (green bacteria) with a human white cell. The bacteria shown is strain MRSA252, a leading cause of hospital-associated infections in the United States and United Kingdom. Credit: NIAID

#### Question 12 of 25

A 30 year-old HIV positive South African woman presents to the emergency department with a 12 day history of fever and headache. On examination she is found to have a 6th nerve palsy, papilloedema and erythematous skin papules across her torso. She is not on any medication.

Investigations:

CD4 count 90 cells / mm<sup>3</sup>

CT head: Normal

What is the most appropriate immediate management?

[Intravenous ceftriaxone16%](#) [Anti-retroviral therapy22%](#) [Rifampicin, isoniazid, pyrazinamide & ethambutol12%](#) [Intravenous albendazole & hydrocortisone18%](#) [Intravenous amphotericin B & flucytosine33%](#)

This is a classical presentation of cryptococcal meningitis - typically there is a sub-acute onset of symptoms and the disease is associated with raised intracranial pressure (leading to the papilloedema and the falsely localising 6th nerve palsy). This raised intracranial pressure (ICP) is thought to be caused by the yeast cells and fungal polysaccharides forming microscopic plugs and blocking CSF resorption in the subarachnoid villi. The best management would be

intravenous anti-fungal agents, such as amphotericin B and flucytosine. Therapeutic lumbar puncture is also advocated to reduce ICP. Anti-retroviral (ARV) therapy should not be started immediately, as there is a very high risk of the patient developing IRIS (immune reconstitution inflammatory syndrome). Instead, ARVs should be delayed for several weeks or months after initiating treatment.

## **HIV: neurocomplications**

### **Focal neurological lesions**

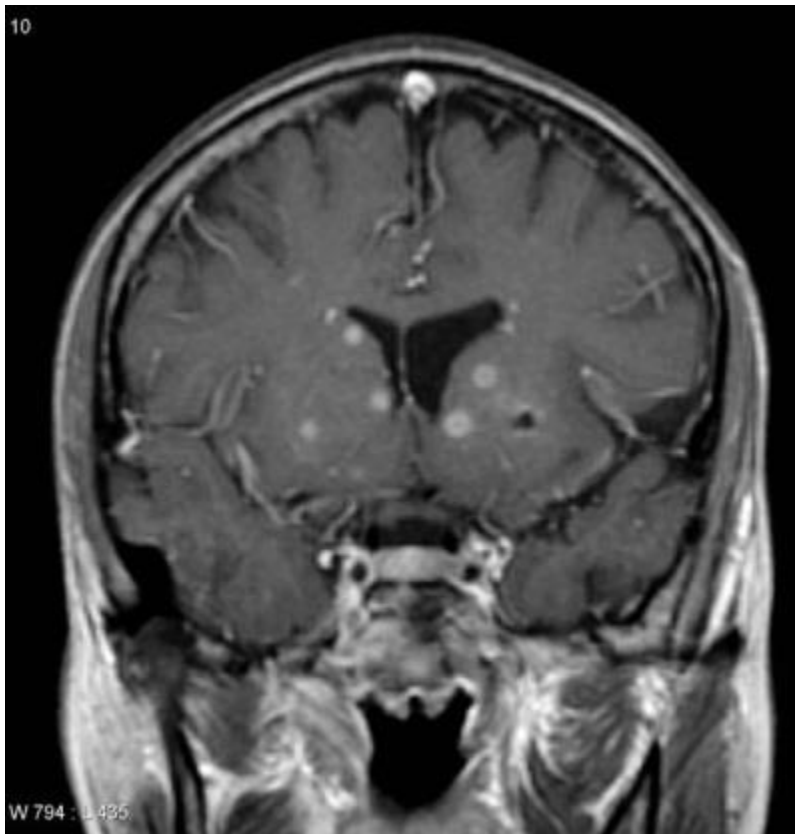
#### **Toxoplasmosis**

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



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Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

#### Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



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Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



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Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. It is clearly important given the vastly different treatment strategies. The table below gives some general differences. Please see the Radiopaedia link for more details.

<b>Toxoplasmosis</b>	<b>Lymphoma</b>
Multiple lesions	Single lesion
Ring or nodular enhancement	Solid (homogenous) enhancement
Thallium SPECT negative	Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

## Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

## *Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

## Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 1 of 13

A 45 year old man presents to the Emergency Department. He told the admitting doctor that he had fallen onto his left hip last night whilst he had been drinking at home. He had extensive bruising around his hip and some bony tenderness and so a hip x-ray was taken.

His x-ray shows no fracture nor bony abnormality, but several 2x4mm specs of calcification are visible in his psoas and thigh muscles.

Later on his wife asks to speak to you in confidence. She states that over the last year her husband's personality has gradually changed and he is sometimes forgetful. He lost his job 3 months ago as an engineer. He had worked for 8 years in Peru on an engineering project in his

thirties. He drinks 8 units of alcohol per day and seems to have had a low mood for several years.

Yesterday he had fallen, lost consciousness, and had a jerking of his arms and legs lasting 1 minute. He had hit his hip on a coffee table and had wet himself. Afterwards he felt tired and lethargic but had refused to go to hospital.

What is the most likely diagnosis?

[HIV dementia 8% Alcohol withdrawal seizure 6% Neurocysticercosis 77% Emboli secondary to calcified aortic valve 5% Primary idiopathic epilepsy 5%](#)

This is neurocysticercosis. It is the most common cause of epilepsy worldwide. Eggs of the *Taenia Solium* tapeworm are ingested, oncospheres hatch and migrate to peripheral sites (classically muscles and brain) and become cysticerci. They may remain asymptomatic or cause inflammatory pathology when the cysticerci die. They eventually become calcified.

Diagnosis is made with MRI or CT imaging. Calcified cysts in skeletal muscle may be found incidentally on x-ray. Serology may be helpful.

Management is with Praziquantel or Aldendazole and prednisolone.

## Helminths

### Nematodes (roundworms)

Worm	Notes	Treatment
	Larvae are present in soil and gain access to the body by penetrating the skin	
<i>Strongyloides stercoralis</i>	Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered	Ivermectin and -bendazoles are used
<i>Enterobius vermicularis</i> (pinworm)	Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms	-bendazoles

Worm	Notes	Treatment
	Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	
<i>Ancylostoma duodenale</i> , <i>Necator americanus</i> (hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova  Transmission by deer fly and mango fly	-bendazoles
<i>Loa loa</i>	Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae Typically develops after eating raw pork	Diethylcarbamazine
<i>Trichinella spiralis</i>	Features include fever, periorbital oedema and myositis (larvae encyst in muscle) Causes 'river blindness'. Spread by female blackflies	-bendazoles
<i>Onchocerca volvulus</i>	Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria Transmission by female mosquito	Ivermectin r <b>IVER</b> blindness = <b>IVER</b> mectin
<i>Wuchereria bancrofti</i>	Causes blockage of lymphatics → elephantiasis Transmitted through ingestion of infective eggs.	Diethylcarbamazine
<i>Toxocara canis</i> (dog roundworm)	Features include visceral larva migrans and retinal granulomas VISCious dogs → blindness Eggs are visible in faeces	Diethylcarbamazine
<i>Ascaris lumbricoides</i> (giant roundworm)	May cause intestinal obstruction and occasional migrate to lung (Löffler's syndrome)	-bendazoles

### Cestodes (tapeworms)

Worm	Notes	Treatment
<i>Echinococcus granulosus</i>	Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers.	-bendazoles



Worm	Notes	Treatment
	Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal)	
<i>Taenia solium</i>	Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
<i>Fasciola hepatica</i> (the liver fluke)	May cause biliary obstruction	Triclabendazole

### Trematodes (flukes)

Worm	Notes	Treatment
<i>Schistosoma haematobium</i>	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
<i>Paragonimus westermani</i>	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs Caused by undercooked fish	Praziquantel
<i>Clonorchis sinensis</i>	Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	

### Question 2 of 13

A 45-year-old man is reviewed in the HIV clinic. He was diagnosed with HIV 25 years ago and has enjoyed good health on highly active antiretroviral treatment until around 4 years ago when he had an episode of *Pneumocystis jirovecii* pneumonia.

Today he is somewhat confused. His partner reports that he has been complaining of headaches for several weeks and has also been uncharacteristically aggressive.

His latest CD4 count is 29 cells/ $\mu$ l. An MRI (T1 C+) is requested:



What is the most appropriate treatment?

[Sulfadiazine + pyrimethamine](#)12% [Sulfadiazine + pyrimethamine + steroids](#)29% [Steroids + methotrexate](#)38% [Rifampicin + isoniazid + pyrazinamide + ethambutol + steroids](#)11% [Amphotericin B](#)10%

The MRI scan demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is also a significant mass effect. These findings in addition to the history are highly suggestive of primary CNS lymphoma. The most appropriate initial treatment is steroids (which should reduce tumour size and hence mass effect) and methotrexate. Other future options include whole brain irradiation and surgery.

You would not expect the enhancement to be homogenous with toxoplasmosis, it is usually in a ring pattern.

**HIV: neurocomplications**

## Focal neurological lesions

### Toxoplasmosis

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## AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

## Question 3 of 13

A 27 week pregnant woman attends her GP with a 12 hour history of a rash. On examination, she has lesions consistent with a diagnosis of chickenpox. Her clinical observations are stable and she is otherwise well.

What would be the recommended management?

[No treatment needed6%Symptomatic treatment only \(antihistamine & calamine lotion\)8%Oral aciclovir 29%Varicella-zoster immunoglobulin \(VZIG\)29%Oral aciclovir & VZIG29%](#)

The development of chickenpox in a pregnant woman is associated with increased morbidity,

including pneumonia, hepatitis and encephalitis. Therefore, pregnant women who develop a chickenpox rash should see their GP immediately.

Oral aciclovir should be prescribed in pregnant women with chickenpox, if they present within 24 hours of the onset of the rash and are 20 weeks gestation or beyond. (Use before 20 weeks can be considered).

Aciclovir reduces the duration of fever and symptomatology of varicella, if commenced within 24 hours of developing the rash. Symptomatic treatment can be used alongside aciclovir.

Pregnant women with severe chickenpox should be referred to hospital for intravenous aciclovir. In addition, a referral to fetal medicine would be necessary (in the above scenario), due to the small risk of fetal varicella syndrome in the first 28 weeks of pregnancy.

It is important to advise anyone with chickenpox to avoid contact with other potentially susceptible people, such as pregnant women and neonates until the last lesions have crusted over (usually 5 days after the onset of the rash).

VZIG has no therapeutic benefit once the rash has started. RCOG Greentop guidelines, Chickenpox in pregnancy.

### **Chickenpox exposure in pregnancy**

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is reactivation of dormant virus in dorsal root ganglion. In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Risks to the mother

- 5 times greater risk of pneumonitis

Fetal varicella syndrome (FVS)

- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

Other risks to the fetus



- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester
- severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

#### Management of chickenpox exposure

- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently checked for varicella antibodies
- if the pregnant woman is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure
- consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

#### Question 4 of 13

A 40-year-old woman is referred to the infectious diseases team after attending her GP practice requesting advice regarding antibiotic prophylaxis for Lyme disease. The patient explains that she is planning on a 2 week long walking holiday in the Lake District National Park in Cumbria, United Kingdom and that she is concerned about the risk associated with receiving tick bites during this period. Lyme disease is a particular concern for the patient as her younger sister had suffered serious neurological complications from the condition secondary to a tick bite in the Scottish Highlands. Concern about contracting Lyme disease herself had prevented her from partaking in her hobby of cross country walking for the past 2 years but she had now decided to confront her fear by undertaking the planned trip. After undertaking research on the Internet, the patient was keen to receive prophylactic antibiotics against *Borrelia* species during her trip.

The patient's past medical history included a diagnosis of breast cancer seven years previously. Following this diagnosis, the patient had undergone a wide local excision of the tumour with postoperative chemotherapy. The patient had been given the all clear from her oncologists after five years and had been subsequently been discharged from follow-up. In addition, the patient had experienced long-standing and, at times, troubling symptoms of irritable bowel syndrome.

The patient took regular hyoscine butylbromide as treatment of her gastrointestinal symptoms. The patient stated that she was allergic to penicillin-based antibiotics. Close questioning on this topic revealed that her adverse reaction to a previous course of penicillin V had been a protracted episode of diarrhoea.

The patient lives with her husband and three teenage children. She was employed full-time as a music teacher. The patient did not smoke cigarettes and consumed approximately 10 units of alcohol per week.

What is appropriate management following the patient's request for antibiotic prophylaxis against Lyme disease during her walking holiday?

[Prescribe amoxicillin for the duration of the patient's holiday4%](#)[Prescribe amoxicillin for immediate use if she receives a tick bite5%](#)[Prescribe doxycycline for the duration of the patient's holiday continued for an additional 10 days after her return home24%](#)[Advice on the prevention and management of tick bites only50%](#)[Prescribe doxycycline for immediate use if she receives a tick bite17%](#)

There is no role for antibiotic prophylaxis against Lyme disease. Simple advice on prevention of tick bites includes wearing clothing that adequately covers the patient's body and the use of insect repellent chemicals. Ticks that have attached themselves should be gently removed using tweezers to minimise the risk of rupturing the tick and potentially releasing infected material.

Individuals showing symptoms of Lyme disease - for example, erythema migrans - following potential exposure to tick bites should be treated with a 14-21 day course of doxycycline or amoxicillin immediately.

Individuals with a history of tick bite but without symptoms of Lyme disease do not normally require either treatment or serological testing. Treatment of asymptomatic individuals who have received a tick bite may be appropriate in certain situations; for example, in individuals who are immunosuppressed or who received tick bites in high-risk regions of the USA.

Duncan C, Carle G, Seaton R. Tick bite and early Lyme borreliosis. *BMJ* 2012;344:e3124.

## **Lyme disease**

Lyme disease is caused by the spirochaete *Borrelia burgdorferi* and is spread by ticks

### **Features**

- early: erythema chronicum migrans + systemic features (fever, arthralgia)
- CVS: heart block, myocarditis
- neuro: cranial nerve palsies, meningitis

### **Investigation**

- serology: antibodies to *Borrelia burgdorferi*. These can take 3-8 weeks before they are detectable

## Management

- doxycycline if early disease. Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
- ceftriaxone if disseminated disease
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

### Question 1 of 9

A 55 year old man attended his General Practitioner to complain of on-going fatigue and lethargy over recent months. He reported experiencing recurrent minor infections meaning that he had rarely been feeling well for any significant length of time. His GP records supported this story with the patient having been prescribed courses of antibiotics for a leg cellulitis, suppurative otitis media and sinusitis (twice) over the past 9 months. The patient reported a good appetite and no recent weight loss, fevers or night sweats. He denied any symptoms of arthritis, skin rashes, photophobia or dry eyes. There were no significant gastrointestinal or genitourinary symptoms.

Past medical history included obesity, hypertension, impaired fasting glucose tolerance and osteoarthritis of the knees. Drug therapy included ramipril 2.5 mg daily, bendroflumethiazide 2.5 mg daily and paracetamol as required. The patient was divorced with two grown up children. He was an ex-smoker who rarely drank alcohol. The patient had recently retired having previously worked as a salesperson for luxury yachts, an occupation that had involved extensive travel around the world.

On examination, the patient was significantly overweight (BMI 36 kg / m<sup>2</sup>). Abdominal examination did not demonstrate any jaundice or signs of chronic liver disease and no lymphadenopathy. Cardiovascular, respiratory and musculoskeletal examination was unremarkable. Given the patients concerns, his General Practitioner arranged some basic blood tests.

Haemoglobin	16.0 g / dL
Mean cell volume	85 fL
White cell count	$5.2 \times 10^9/l$
Neutrophils	$4.2 \times 10^9/l$
Lymphocytes	$0.6 \times 10^9/l$
Monocytes	$0.1 \times 10^9/l$
Eosinophils	$0.1 \times 10^9/l$
Basophils	$0.2 \times 10^9/l$
Platelets	$358 \times 10^9/l$
Urea	6.8 mmol / L

Creatinine	110 micromol / L
Sodium	141 mmol / L
Potassium	3.9 mmol / L
Albumin	34 g / L (reference 35-50)
Alkaline phosphatase	98 U / L (reference (35-100)
ALT	28 U / L (reference 3-36)
Bilirubin	21 micromol / L (reference < 26)
Total protein	85 g / L (reference 60-80)
B12	355 pmol / L (reference 74-516)
Folate	30 nmol / L (reference 7-36)
Serum immunoglobulins	Normal electrophoresis strip

Comparison with a routine blood test taken 6 months previously had shown a similar full blood count differential.

What is the most appropriate next line investigation?

[Human immunodeficiency virus antibody testing69%Anti-nuclear antibody8%Rheumatoid factor4%Epstein-Barr virus serology10%Serum angiotensin-converting enzyme9%](#)

The patient has a persistent lymphopenia, raised total protein and low albumin in the setting of fatigue and recurrent minor infections. These findings could all be explained by nascent HIV infection. The patients history of international travel may place him at increased risk of HIV infection and a full sexual history would be required.

The other investigations listed would assess for other possible causes of isolated lymphopenia, however there is no clinical evidence of connective tissue disease, EBV infection or sarcoidosis to

Brass D, McKay P, Scott F. Investigation an incidental finding of lymphopenia. BMJ 2014;348:g1721.

## **HIV: seroconversion**

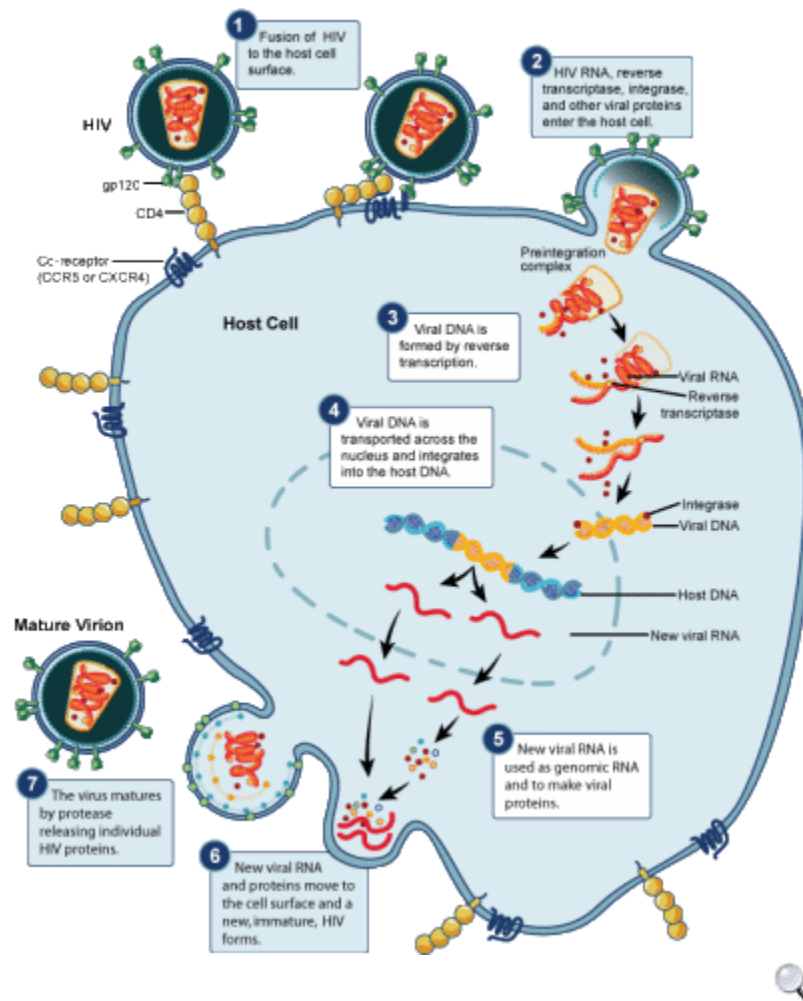
HIV seroconversion is symptomatic in 60-80% of patients and typically presents as a glandular fever type illness. Increased symptomatic severity is associated with poorer long term prognosis. It typically occurs 3-12 weeks after infection

Features

- sore throat
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea
- maculopapular rash
- mouth ulcers
- rarely meningoencephalitis

## Diagnosis

- antibodies to HIV may not be present
- HIV PCR and p24 antigen tests can confirm diagnosis



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

## Question 2 of 9

A 38-year-old woman presents to her HIV clinic for her 6-monthly review having had her routine blood tests two weeks prior to her clinic visit. She has diagnosed with HIV seven years ago and has been stable on antiretroviral therapy since then. Her other medical problems include asthma which is well controlled. She reports generally good compliance with her medications but has unfortunately missed two of her treatment doses as she was on a weekend holiday and forgot to take her tablets with her. She feels well in herself.

Blood tests:

	Today	Two weeks ago	One year ago
HIV viral load	110 copies/ml	<50 copies/ml	<50 copies/ml
CD4 count	983 cells/mm <sup>3</sup>	912 cells/mm <sup>3</sup>	Not tested

How should she be further investigated?

[Urgent CD4 count4%](#)[Urgent viral resistance testing20%](#)[Urgent HIV-1 and HIV-2 serology8%](#)[Repeat viral load in one month45%](#)[Routine viral load and CD4 count in six months23%](#)

The question describes a possible viral blip, a single viral load that is detectable but less than 200 copies/ml. This is a common feature in chronic HIV management and does not imply failure of treatment. However, good compliance should be reinforced and viral load should be repeated within one month so exclude virological failure or rebound. A CD4 count would not be reassuring in this circumstance as if normal there could still be a rebound happening. Serology only aids diagnosis. Viral resistance testing is useful in order to determine the cause of virological failure. Routine monitoring is not appropriate as a viral rebound will need to be excluded.

HIV monitoring

HIV, once stable, should be monitored with a viral load every six months and CD4 counts annually at least once virological suppression, defined as sustained viral load less than <50 copies/ml, is established. If the viral load increases to between 50-200 copies/ml on a single sample this is defined as a viral blip and is unlikely to be significant, but a viral load should be re-tested within one month. If a viral load above >200 copies/ml is sustained this is a virological rebound and can imply failure. This can be due to new viral resistance, and, if suspected, would need resistance testing.

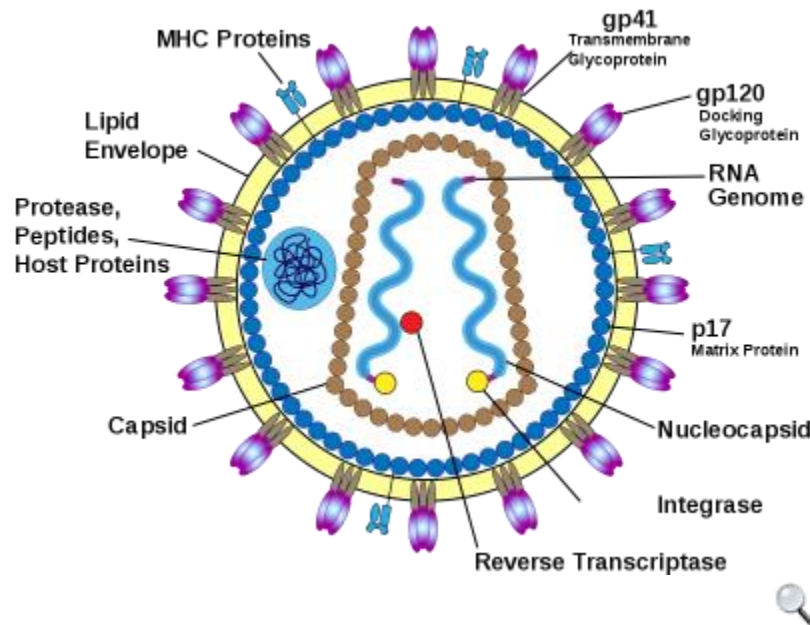
Source:

'BHIVA Guidelines for the Treatment of HIV-1-positive Adults with Antiretroviral Therapy 2015.' BHIVA. Aug. 2016.

## HIV: the virus

### Basics

- HIV is a RNA retrovirus of the lentivirus genus (lentiviruses are characterized by a long incubation period)
- two variants - HIV-1 and HIV-2
- HIV-2 is more common in west Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS



### Basics structure

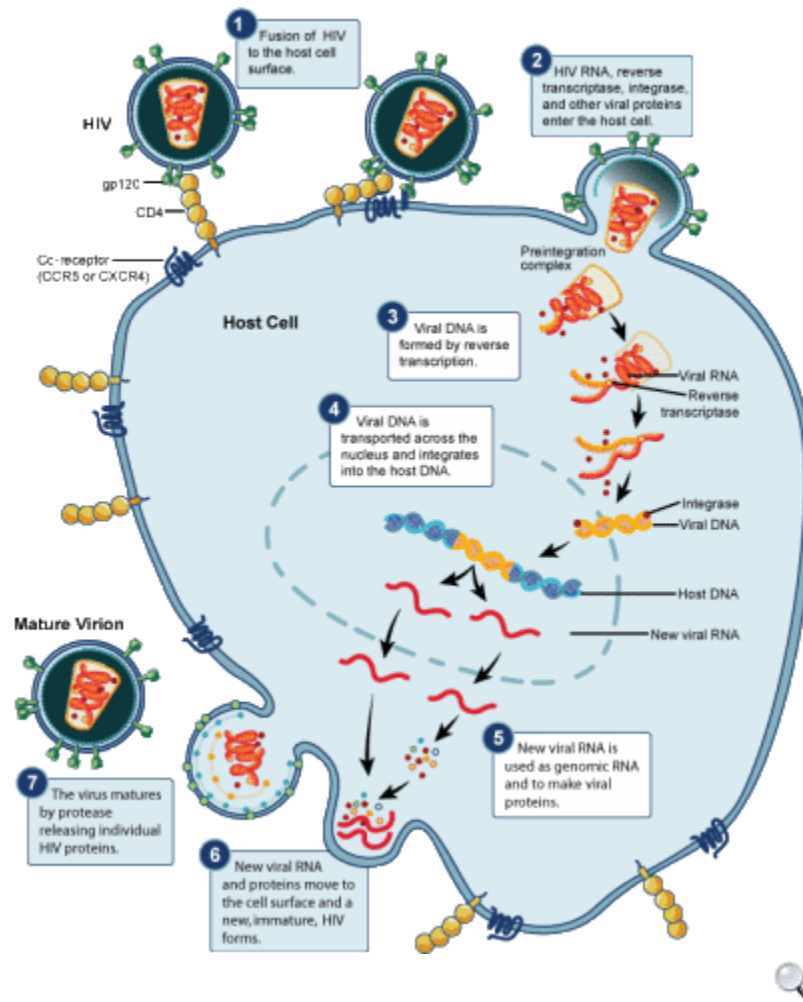
- spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24
- a matrix composed of viral protein p17 surrounds the capsid
- envelope proteins: gp120 and gp41
- pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease

### Cell entry

- HIV can infect CD4 T cells, macrophages and dendritic cells
- gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages
- mutations in CCR5 can give immunity to HIV

## Replication

- after entering a cell the enzyme reverse transcriptase creates dsDNA from the RNA for integration into the host cell's genome



An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID



### Question 3 of 9

A 23-year-old student presented to his GP with fever and epistaxis. The fever had started 6 days earlier. It had been associated with a headache and malaise. Following clinical examination his doctor prescribed him amoxicillin which he took for 3 days but without any improvement. He later became so ill that he refused to eat and started to vomit.

His history included mumps at the age of nine. His father had been diagnosed with liver cirrhosis 2 years ago due to excessive alcohol consumption. He is a regular smoker for the last 10 years and lives in the dorm. Two weeks earlier he had been in rural Central Africa as a reporter covering the conflict there. He denied being vaccinated for any disease before going there but did take anti-malarial tablets.

On examination he appeared ill. His temperature was 38°C. He was jaundiced. Eye examination revealed conjunctival hemorrhages on both eyes. All other systems were normal.

The following investigations had been requested:

Hb	13 g/dl
platelets	$170 \times 10^9/l$
WBC	$4 \times 10^9/l$
MCV	85 fl
MCH	0.4 fmol/cell
MCHC	20 mmol/l
Na+	135 mmol/l
K+	4 mmol/l
Creatinine	80 $\mu$ mol/l
Urea	3 mmol/l
ESR	60 mm/hr
Alkaline phosphatase	100 IU/l
Alanine transaminase	400 IU/l
Aspartate transaminase	200 IU/l
Bilirubin	25 $\mu$ mol/l (direct 18 $\mu$ mol/l)
Serum albumin	40 g/l
Prothrombin time	prolonged
Partial thromboplastin time	prolonged
Urine analysis	Albumin + ,acetone ++ ,bile pigment ++,urinary urobilinogen +
Thick Blood film for malaria	negative

What is the most likely diagnosis?

[Yellow fever46%Primary sclerosing cholangitis4%Leptospirosis22%Falciparum malaria6%Dengue fever22%](#)

Yellow fever is endemic around the equator mainly in Africa. It is transmitted by the *Aedes* mosquitoes there. Characteristically the patient presents with fever and constitutional symptoms. Jaundice is a main clinical sign associated most of the times with conjunctival injection. Other important clinical signs are relative bradycardia, and hemorrhagic diathesis. The cause of death is due to multi-organ failure.

Blood tests generally show leucopenia with predominant neutropenia but this is not specific. Liver enzymes are elevated most of the time. Diagnosis depends on a high degree of suspicion for the disease and but also more important on serology which is highly specific for this lethal condition.

Treatment is mainly supportive.

Primary sclerosing cholangitis could present with fever and jaundice. This would happen in the context of ascending cholangitis (fever + pain + jaundice) with a long history of abdominal discomfort. Liver profile would reflect obstructive changes.

Malaria should be excluded in any patient who had traveled to an endemic area and developed fever. The picture in our patient was not typical and the blood film had been negative for malaria parasites. However one has to keep it in mind if the clinical picture fits. In that case one needs to repeat the blood film and to order serology.

Leptospirosis is a consideration here. But it usually responds to antibiotics. Liver enzymes would generally be more mildly elevated.

Dengue fever mainly presents with headache, fever and rash. It is mainly endemic in South East Asia.

## **Yellow fever**

Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

### **Basics**

- spread by *Aedes* mosquitos
- incubation period = 2 - 14 days

### **Features**

- may cause mild flu-like illness lasting less than one week
- classic description involves sudden onset of high fever, rigors, nausea & vomiting. Bradycardia may develop. A brief remission is followed by jaundice, haematemesis, oliguria
- if severe jaundice, haematemesis may occur
- Councilman bodies (inclusion bodies) may be seen in the hepatocytes

#### Question 4 of 9

A 65-year-old man is undergoing treatment in the intensive care unit. He had presented 8 days previously after suffering a seizure at home. He had been unable to give a coherent history at the time of presentation but his family had reported he had been unwell for about two weeks. Initial symptoms included a fever, myalgia, anorexia and an intense itching of his left arm.

Subsequently, the patient had developed progressive confusion and agitation and was incoherent by the time of presentation to hospital. The patient was a long-term resident of the UK, but had made a trip back to his native India around 6 months previously. During that trip, his wife recalled the patient being bitten by a dog in his family village, although the wound had been minor and healed without incident after basic first aid. Medical history was otherwise fairly unremarkable, including hypertension, tablet-controlled type 2 diabetes and gout.

At presentation, the patient had been noted to be highly agitated and disorientated. Hypersalivation was noted and patient had been refusing to eat or drink. Examination had been limited by the patient's agitation but no overt focal neurological symptoms were noted in the cranial nerve or peripheral nervous examination. After the patient had been sedated, it was noted that striking a large muscle group with a tendon hammer led to few seconds of mounding of the muscle.

CSF protein	457 g / dL
CSF Microscopy	NAD
CSF rabies virus neutralising antibodies	Not detected
Serum rabies virus neutralising antibodies	Detected

At the present time, the patient is receiving end-of-life care. He is sedated and appears comfortable secondary to midazolam delivered by a syringe driver. His family wish to be present at his bedside.

What is the appropriate personal protection for healthcare workers and family members to use while in contact with the patient?

[High isolation12%Standard precautions52%Respiratory isolation13%Reverse isolation7%Biocontainment precautions16%](#)

The patient is unfortunately suffering from rabies. His presentation is consistent with the classical form of 'furious rabies', with fever, agitation, confusion and seizures. The response of the patient's muscles to being struck with a tendon hammer described in the question is called myoedema and is suggestive of rabies. Neutralising serum antibodies may be detected 7-8 days after the onset of symptoms but are only occasionally found in CSF. An alternative form of the disease ('paralytic rabies') is also known, featuring an ascending paralysis or symmetric quadriparesis.

The patient presumably contracted the disease on his previous trip to India when he was bitten by a dog. An incubation period of 6 months is not uncommon (mean incubation time 274 days in one study) with cases reported with incubation time up to 10 years. By the time neurological symptoms have taken hold, death is inevitable in unimmunised patients. This highlights the need for appropriate vaccination for individuals travelling to high-risk areas, as well as post-exposure vaccination and immunoglobulin administration.

Lyssaviruses such as rabies cannot cross intact skin and humans are regarded as an end-host (outside of transplantation-associated transmission). Therefore, only standard infection-prevention precautions such as gloves and gowns are required.

High isolation refers to the extreme precautions taken with high-transmissible and dangerous infections such as Ebola. Respiratory isolation requires the use of a mask to prevent droplet transmission by the respiratory route. Reverse isolation refers to techniques required to prevent external pathogens causing harm to an immunosuppressed patient. Biocontainment refers to laboratory biosafety techniques required when handling highly pathogenic organisms.

Crowcroft N, Thampi N. The prevention and management of rabies. *BMJ* 2015;350:g7827.

## **Rabies**

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus (specifically a lyssavirus) and has a bullet-shaped capsid. The vast majority of cases are caused by dog bites but it may also be transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Rabies is estimated to still kill around 25,000-50,000 people across the world each year. The vast majority of the disease burden falls on people in poor rural areas of Africa and Asia. Children are particularly at risk.

## **Features**

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at-risk countries:

- the wound should be washed
- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination. If possible, the dose should be administered locally around the wound

If untreated the disease is nearly always fatal.

#### Question 5 of 9

A 35-year-old male attends clinic with a new diagnosis of chronic hepatitis B infection. He gives a history of unprotected sex with multiple sexual partners in the two years. His blood tests show him to be HIV, HCV antibody and HBeAg negative. The most recent liver function tests are shown below. On examination, he has no evidence of decompensated liver disease.

Bilirubin	18µmol/L
ALT	52iu/L
AST	38iu/L
ALP	190iu/L
Albumin	30g/L
Protein	93g/L
HBV viral load 2,000IU/mL	

Which one of the following treatment options should be considered first line?

[Peginterferon alpha 2a and entecavir29%Entecavir8%Peginterferon alpha 2a40%Tenofovir disoproxil10%Entecavir and tenofovir disoproxil13%](#)

Peginterferon alpha 2a is the first line treatment for adults with HBeAg-negative chronic hepatitis B with compensated liver disease. Tenofovir disoproxil or entecavir are second line treatment in those who have detectable HBV DNA after treatment with peginterferon alpha 2a.

Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults (2013)

## **Hepatitis B**

Hepatitis B is a double-stranded DNA hepadnavirus and is spread through exposure to infected blood or body fluids, including vertical transmission from mother to child. The incubation period is 6-20 weeks.

The features of hepatitis B include fever, jaundice and elevated liver transaminases.

Complications of hepatitis B infection

- chronic hepatitis (5-10%)
- fulminant liver failure (1%)
- hepatocellular carcinoma
- glomerulonephritis
- polyarteritis nodosa
- cryoglobulinaemia

Immunisation against hepatitis B (please see the Greenbook link for more details)

- children born in the UK are now vaccinated as part of the routine immunisation schedule. This is given at 2, 3 and 4 months of age
- at risk groups who should be vaccinated include: healthcare workers, intravenous drug users, sex workers, close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, chronic liver disease patients
- contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology
- around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression
- testing for anti-HBs is only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease. In these patients anti-HBs levels should be checked 1-4 months after primary immunisation
- the table below shows how to interpret anti-HBs levels:

Anti-HBs level (mIU/ml)	Response
> 100	Indicates adequate response, no further testing required. Should still receive booster at 5 years
10 - 100	Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required
< 10	Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

### Management of hepatitis B

- pegylated interferon-alpha used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy
- whilst NICE still advocate the use of pegylated interferon first-line other antiviral medications are increasingly used with an aim to suppress viral replication (not in a dissimilar way to treating HIV patients)
- examples include tenofovir and entecavir

### Question 6 of 9

A 70-year-old female was admitted to the emergency department from a nursing home due to a progressive decline in her level of consciousness over the past two days. Her carer mentioned that she had been complaining of a burning sensation while urinating associated with a low-grade fever for the last week. Blood investigations showed:

Na<sup>+</sup> 130 mmol/l  
K<sup>+</sup> 3.6 mmol/l  
Urea 13 mmol/l  
Creatinine 130 µmol/l

Urine dipstick showed increase leukocytes and nitrites. Urine culture showed a growth of extended-spectrum B-lactamase (ESBL) - producing *Escherichia coli*.

What is the first line treatment?

[Ciprofloxacin19% Ceftriaxone9% Meropenem59% Methoprim6% Aztreonam7%](#)

The regular use of B-lactam antibiotics for urinary tract infection has resulted in the emergence of new strains of bacteria that are resistant to these antibiotics. ESBL is one of the most problematic strains that is usually difficult to treat.

First line antibiotics are still carbapenems (imipenem, meropenem, ertapenem, doripenem).

Giving these antibiotics may further increase resistance so the advice is not to give antibiotics unless there are clinical signs and symptoms of a urinary tract infection.

Source:

Shaikh, S., Fatima, J., Shakil, S., Rizvi, S. and Kamal, M. (2015). Antibiotic resistance and extended-spectrum beta-lactamases: Types, epidemiology and treatment. Saudi Journal of Biological Sciences, 22(1), pp.90-101.

### ***Escherichia coli***

*Escherichia coli* is a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

*E. coli* infections lead to a variety of diseases in humans including:

- diarrhoeal illnesses
- UTIs
- neonatal meningitis

### **Serotypes**

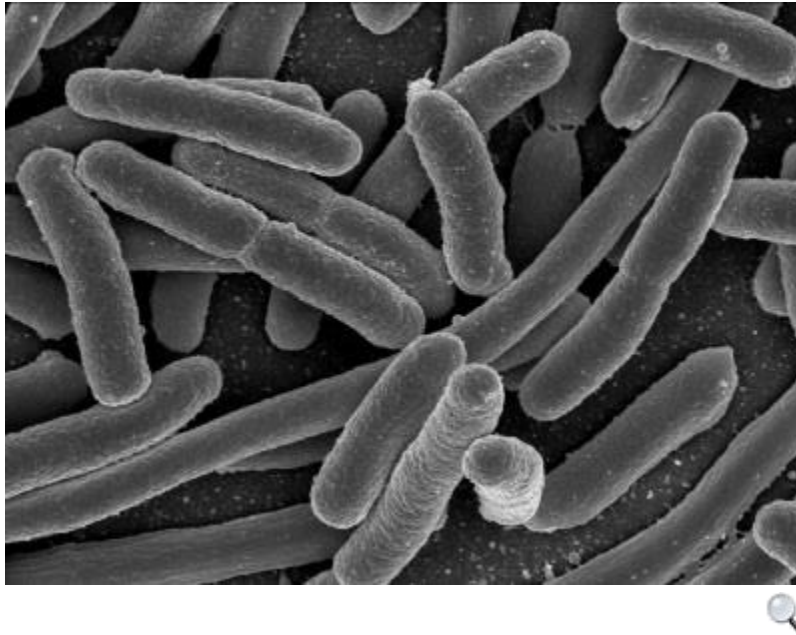
*E. coli* may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to <i>E. coli</i> is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

*E. coli* O157:H7 is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It



has a high mortality rate and can be complicated by haemolytic uraemic syndrome. It is often spread by contaminated ground beef.



Scanning electron micrograph of *Escherichia coli*, grown in culture and adhered to a cover slip.  
Credit: NI

#### Question 7 of 9

A 23 year-old student presents with a febrile illness, seven days after return from holiday in Thailand. He delayed seeking medical attention because he thought it was 'just a virus', and he had experienced similar self-limiting symptoms when travelling to Vietnam several years earlier. He did not take malaria prophylaxis due to a previous adverse reaction to mefloquine. The illness began two days after his return, when he recorded his temperature at 38.4°C. He also complains of severe generalised joint pains and headache which he describes as 'behind the eyes'. Today he has developed nosebleeds and when he brushed his teeth this morning he noticed that his gums bled.

On examination his temperature is 38.2°C and there is a widespread macular rash with islands of sparing. There are some petechial haemorrhages on the limbs. Cardio-respiratory examination is unremarkable except for tachycardia of 114. Blood pressure is 123/79 mmHg. On palpation of the abdomen you discover tender hepatomegaly. Neurological examination is unremarkable.

On application of a tourniquet to take a blood sample you notice that the area under the tourniquet has become bruised.

Results of blood tests are as follows:

Hb                      14.1 g/dl

MCV 94.2 fl  
Haematocrit 0.57  
Platelets  $23 \times 10^9/l$   
WCC  $6.1 \times 10^9/l$

Na<sup>+</sup> 134 mmol/l  
K<sup>+</sup> 4.6 mmol/l  
Urea 3.8 mmol/l  
Creatinine 80  $\mu$ mol/l

ALT 64 IU/l  
ALP 78 IU/l  
Bilirubin 13 mol/l  
Albumin 28 g/l

Rapid Malaria test Negative  
Thick and thin blood films Pending

What is the most likely diagnosis?

[Non-falciparum malaria 6% Dengue haemorrhagic fever 79% Lassa fever 7% Meningococcal septicaemia 4% HIV seroconversion 3%](#)

This is a viral haemorrhagic fever, and the clinical picture is classic for dengue. The disease is endemic in South-East Asia. A defective immune response in secondary infections means that individuals who have been infected with one viral serotype may develop more severe disease when later infected with a different serotype. This patient may have developed self-limiting dengue fever on a previous trip to Vietnam, and now has secondary infection.

Dengue fever typically begins 7-10 days after infection with a rapid onset of fever, severe myalgia, and retro-orbital headache. A maculopapular rash with islands of sparing is characteristic. In the majority of cases there is self-resolution after 2-7 days. In a proportion of cases however, especially in secondary infection, the disease progresses to a more fulminant form known as dengue haemorrhagic fever. There is widespread vascular breakdown, with easy bleeding and bruising. Thrombocytopaenia is typical. Plasma leakage results in haemoconcentration, raising the haemocrit, and loss of plasma proteins into the extracellular space is reflected by the low albumin. The liver is often enlarged and tender, with deranged liver function tests. In severe cases this progresses to circulatory collapse and dengue shock syndrome. Diagnosis is by PCR (polymerase chain reaction) during the initial febrile phase and serology during the later stages. Management is supportive.

Non-falciparum malaria includes disease caused by *Plasmodium vivax* and *ovale*, and to a lesser extent *malariae* and *knowlesi*. *Vivax* is common in Thailand and typically causes less severe disease. Most malaria rapid diagnostic tests are antigen assays that detect only falciparum. Microscopy is the only way to confirm or exclude the diagnosis.

Lassa fever is a viral haemorrhagic fever endemic to West Africa.

Meningococcal septicaemia is a possibility, although one would expect him to be more unwell after five days of disease.

HIV seroconversion illness does not commonly cause bleeding manifestations.

## Dengue fever

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

### Basics

- transmitted by the *Aedes aegypti* mosquito
- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

### Features

- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

Treatment is entirely symptomatic e.g. fluid resuscitation, blood transfusion etc

A 45-year-old male from Afghanistan presents with a rash all over his body. He describes the rash and suggests that it was initially multiple specks of light skin that were not raised or roughened. they have now progressed to plaques, some of which have become nodular.

He is otherwise well and his past medical history is significant only for the successful treatment of visceral leishmaniasis in his home country some 5 years ago.

What is the most likely underlying diagnosis?

[Leprosy 23% HIV 5% Post kala azar dermal leishmaniasis \(PKDL\) 60% Histoplasmosis 4% Pityriasis versicolor 9%](#)

This is a classic description of post kala azar dermal leishmaniasis (PKDL) from an area where the disease is endemic. Leishmaniasis can manifest as cutaneous, muco-cutaneous and visceral disease. PKDL is a chronic skin condition that arises after the treatment of visceral disease. The skin condition can arise months or years after successful treatment and often presents with erythematous or hypo-pigmented macules that may progress to become nodular. Clinically the lesions look very similar to pityriasis versicolour, however this has a predilection for the chest and back and is likely to have a scaly appearance rather than nodular. Perhaps the most important differential is leprosy and lesions should be tested for anaesthesia which would be strongly indicative for leprosy over PKDL.

Although HIV can cause a myriad of skin pathology there is nothing given in the question to make this a likely diagnosis and the best answer is therefore PKDL.

## **Leishmaniasis**

Leishmaniasis is caused by the intracellular protozoa *Leishmania*, usually being spread by sand flies. Cutaneous, mucocutaneous leishmaniasis and visceral forms are seen

### **Cutaneous leishmaniasis**

- caused by *Leishmania tropica* or *Leishmania mexicana*
- crusted lesion at site of bite
- may be underlying ulcer

### **Mucocutaneous leishmaniasis**

- caused by *Leishmania braziliensis*
- skin lesions may spread to involve mucosae of nose, pharynx etc

### Visceral leishmaniasis (kala-azar)

- mostly caused by *Leishmania donovani*
- occurs in the Mediterranean, Asia, South America, Africa
- fever, sweats, rigors
- massive splenomegaly. hepatomegaly
- poor appetite\*, weight loss
- grey skin - 'kala-azar' means black sickness
- pancytopenia secondary to hypersplenism

\*occasionally patients may report increased appetite with paradoxical weight loss

### Question 9 of 9

A 45 year old man is diagnosed with HIV following attendance at Genitourinary clinic.

As part of his routine HIV work up his HLA B\*5701 result is reported as positive.

Which drug will not be included in his ART regimen as a result of this information?

[Tenofovir 16%](#) [Emtricitabine 20%](#) [Lamivudine 16%](#) [Stavudine 10%](#) [Abacavir 38%](#)

Abacavir can cause a severe and sometimes fatal hypersensitivity reaction. It is a cell mediated delayed hypersensitivity reaction which occurs around 6 weeks after starting treatment. Symptoms are of fever, rash, malaise and gastrointestinal symptoms.

Patients without HLA B\*5701 are highly unlikely to develop hypersensitivity. Those with the HLA B\*5701 allele have a 50% risk and therefore in these individuals abacavir should be avoided.

It is therefore routine to test HLA B\*5701 status on all newly diagnosed patients with HIV.

### **HIV: anti-retrovirals**

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start HAART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

#### Entry inhibitors (CCR5 receptor antagonists)

- maraviroc, enfuvirtide
- prevent HIV-1 from entering and infecting immune cells by blocking CCR5 cell-surface receptor

#### Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

#### Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

#### Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

#### Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

## Endocrinology

### Question 1 of 214

An elderly male presents with a 2 week history of breathlessness. His past medical history includes diet-controlled type 2 diabetes, ischaemic heart disease, hypothyroidism and depression. His medication list includes levothyroxine, aspirin, simvastatin, ramipril, bisoprolol and citalopram. Observations on presentation to Emergency Department are as follows: respiratory rate 26/min, saturations 94% (on 4 litres oxygen via Venturi), heart rate 80 beats per minute, blood pressure 156/82 mmHg. Auscultation demonstrates crackles at the left base with no wheeze. The abdomen is soft and non-tender. There is no oedema peripherally.

Blood results on admission are provided below:

Hb	134 g/l
Platelets	$172 \times 10^9/l$
WBC	$13.3 \times 10^9/l$
Na <sup>+</sup>	128 mmol/l
K <sup>+</sup>	5.1 mmol/l
Urea	13 mmol/l
Creatinine	178 $\mu$ mol/l
Serum osmolality	220 mosm/kg
Urinary sodium	50 mEq/l

What is the most likely cause of hyponatraemia?

[Hypothyroidism](#)6%[Chronic kidney disease](#)6%[Addison's disease](#)11%[Salt-losing nephropathy](#)14%[Syndrome of inappropriate antidiuretic hormone \(SIADH\)](#)63%

This question demonstrates a common scenario in clinical practice. Management of hyponatraemia first requires clarification of fluid status (clinical hypovolaemia, euvolaemia or hypervolaemia), as differentials are influenced by this. This patient's history, examination findings and haemodynamic parameters are consistent with clinical euvolaemia.

Differentials for euvolaemic hyponatraemia would include hypothyroidism and SIADH. There are no clinical features suggestive of the former. Findings are consistent with community-acquired pneumonia with associated SIADH. This is confirmed by the presence of reduced serum osmolality and high urinary sodium. Measurement of urinary sodium concentration is a useful adjunct in helping to differentiate between hyponatraemia secondary to hypovolaemia and SIADH. With SIADH (and salt-wasting syndrome), the urinary sodium is high. With hypovolaemia, the urinary sodium is typically low.

## SIADH: causes

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

### Causes of SIADH

Category	Examples
Malignancy	<ul style="list-style-type: none"><li>• <b>small cell lung cancer</b></li><li>• also: pancreas, prostate</li></ul>
Neurological	<ul style="list-style-type: none"><li>• stroke</li><li>• subarachnoid haemorrhage</li><li>• subdural haemorrhage</li><li>• meningitis/encephalitis/abscess</li></ul>
Infections	<ul style="list-style-type: none"><li>• tuberculosis</li><li>• pneumonia</li></ul>
Drugs	<ul style="list-style-type: none"><li>• sulfonylureas*</li><li>• SSRIs, tricyclics</li><li>• carbamazepine</li><li>• vincristine</li><li>• cyclophosphamide</li></ul>
Other causes	<ul style="list-style-type: none"><li>• positive end-expiratory pressure (PEEP)</li><li>• porphyrias</li></ul>

### Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

\*the BNF states this has been reported with glimepiride and glipizide.



### Question 2 of 214

A 43-year-old man is referred by his GP with a 4 week history of a lump appearing on the right side of his neck. The lump is roughly 7 mm and is located on the right side of the thyroid gland, in the anterior triangle. It does not move when the patient sticks out his tongue, but it does move on swallowing. There is no history of weight loss or night sweats.

Blood tests are performed and reveal:

Hb	12.9 g/l
Platelets	$210 \times 10^9/l$
WBC	$6.0 \times 10^9/l$
Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	3.9 mmol/l
Urea	4.1 mmol/l
Creatinine	33 $\mu$ mol/l

What is the most appropriate first-line investigation?

[Radioisotope scan of thyroid19%](#)[Magnetic resonance scan of head and neck4%](#)[Excision biopsy4%](#)[Fine needle aspiration biopsy14%](#)[Ultrasound scan of thyroid59%](#)

High-resolution ultrasound scanning is an ideal first-line initial imaging investigation for most neck lumps. Because most lesions in the neck are site-specific, once a lesion has been located, specific ultrasound features can be used to establish the diagnosis.

## Thyrotoxicosis

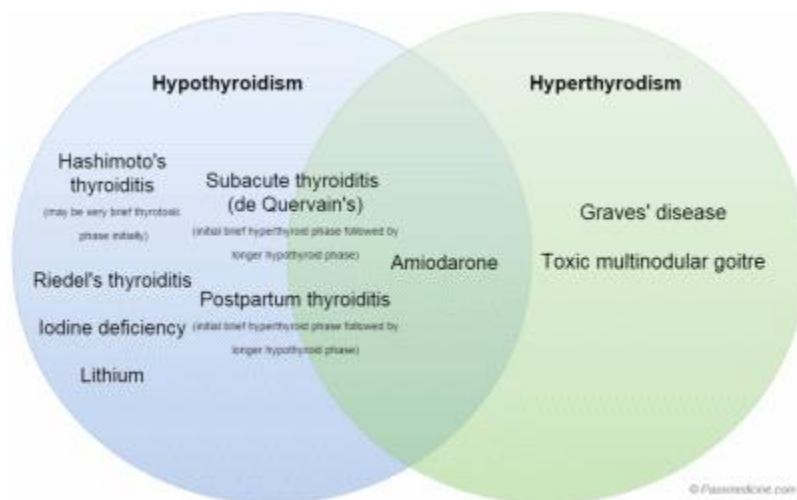
Graves' disease accounts for around 50-60% of cases of thyrotoxicosis.

Causes

- Graves' disease
- toxic nodular goitre
- acute phase of subacute (de Quervain's) thyroiditis
- acute phase of post-partum thyroiditis
- acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- amiodarone therapy

## Investigation

- TSH down, T4 and T3 up
- thyroid autoantibodies
- other investigations are not routinely done but includes isotope scanning



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

### Question 5 of 214

You are reviewing a 57 year-old gentleman in the diabetes outpatient clinic. He has type 2 diabetes mellitus and is currently taking metformin 850mg three times a day and gliclazide 80mg once daily.

On further questioning he admits having frequent hypoglycaemic episodes at night that distress him as he lives alone. His BMI is calculated at 30.3 kg/m<sup>2</sup>, HbA1c 7.8% (62 mmol/mol) and his co-morbidities include congestive cardiac failure.

How would you change his diabetic treatment?

[Stop gliclazide, start insulin9%Add exenatide8%Add sitagliptin to current regimen8%Stop gliclazide, start pioglitazone6%Stop gliclazide, start sitagliptin69%](#)

The NICE guidance on the management of type 2 diabetes mellitus:

- This gentleman has been started on metformin and a sulphonyurea as first line therapy.
- He is having frequent hypoglycaemic episodes secondary to his sulphonylurea and yet control remains poor, HbA1c 7.8% (62 mmol/mol)
- Pioglitazone is contraindicated due to his congestive cardiac failure.
- A DPP-4 inhibitor such as sitagliptin would be a sensible option, the sulphonylurea should be stopped to prevent hypoglycaemia.

## **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

### **Dietary advice**

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

### **HbA1c targets**

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

Practical examples

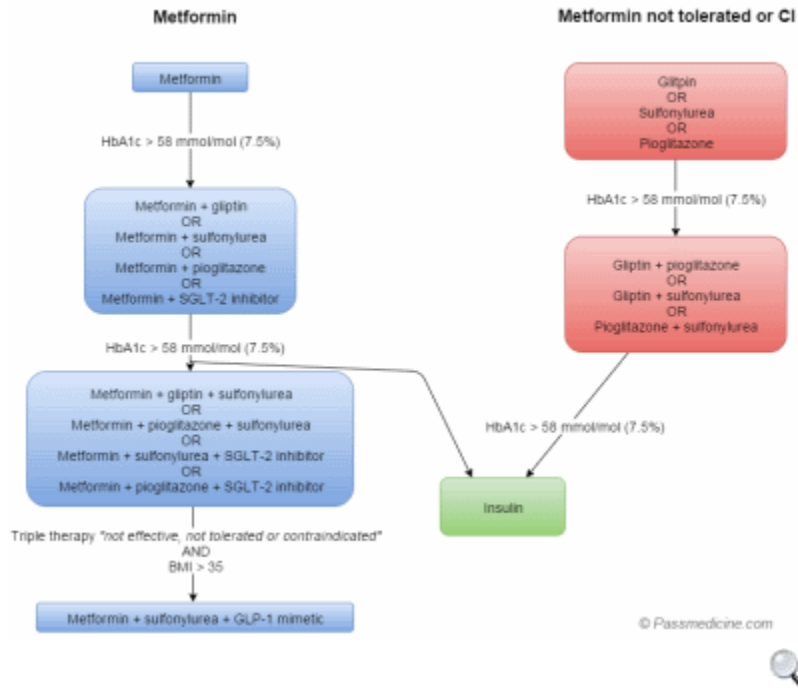
- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

## Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



### Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
  - → SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  - → metformin + gliptin + sulfonylurea
  - → metformin + pioglitazone + sulfonylurea
  - → metformin + sulfonylurea + SGLT-2 inhibitor
  - → metformin + pioglitazone + SGLT-2 inhibitor
  - → OR insulin therapy should be considered

### Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
  - → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or

- → BMI < 35 kg/m<sup>2</sup> and for whom insulin therapy would have significant occupational implications or

weight loss would benefit other significant obesity-related comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

### Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

### Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

### Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: *'Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

### Risk factor modification

#### Blood pressure

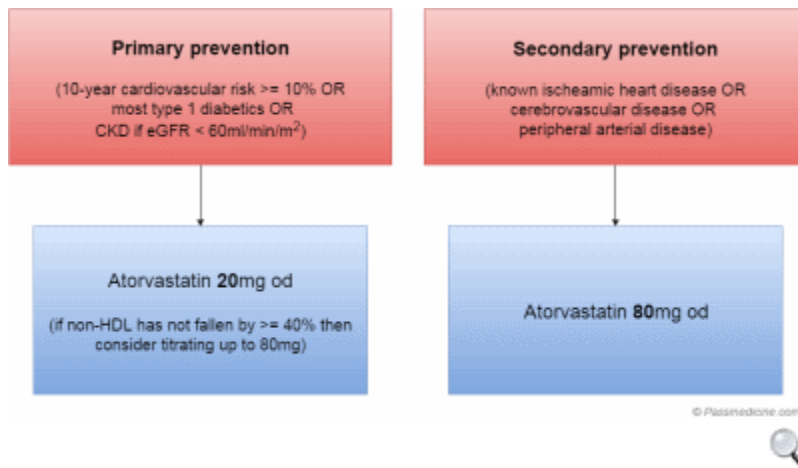
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

### Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



Graphic showing choice of statin.

\*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

### Question 6 of 214

A 20-year-old female admits to abusing codeine and diclofenac, up to 30 tablets per day. She attends the emergency department demanding help with her addiction. Her baseline bloods include:

pH 7.28  
PCO<sub>2</sub> 2.9 kPa  
PO<sub>2</sub> 8.5 kPa  
HCO<sub>3</sub><sup>-</sup> 16 mmol/l

Na<sup>+</sup> 130 mmol/l  
K<sup>+</sup> 6 mmol/l  
Cl<sup>-</sup> 110 mmol/l  
HCO<sub>3</sub><sup>-</sup> 16 mmol/l

What is the most likely diagnosis?

[Lactic acidosis9% Type 1 renal tubular acidosis13% Type 2 renal tubular acidosis14% Type 4 renal tubular acidosis58% Ketoacidosis5%](#)

Type 4 renal tubular acidosis is due either to a deficiency of aldosterone or to a resistance to its effects.

Causes include:

- Aldosterone deficiency (hypoaldosteronism): Primary vs. hyporeninaemic
- Aldosterone resistance
- → 1. Drugs: Non-steroidal anti-inflammatories, angiotensin converting enzyme inhibitors, angiotensin 2 receptor blockers, eplerenone, spironolactone, trimethoprim, pentamidine
- → 2. Pseudohypoaldosteronism

## **Renal tubular acidosis**

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete H<sup>+</sup>) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy





© Image used on license from [Radiopaedia](#)

Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased  $\text{HCO}_3^-$  reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

#### Question 1 of 207

A 30-year-old south Asian woman is admitted to the accident and emergency department with abdominal pain. She is thought to be constipated. Initial blood results with subsequent tests are listed below. Urine is clear and an ECG performed is normal. Examination is unremarkable with no oedema, and blood pressure 105/68 mmHg.

pH 7.250

Bicarbonate 18.0 mmol/l

Base excess 8.0 mmol/l

Anion gap Normal

Potassium 7.2 mmol/l

Creatinine 56 mmol/l

Glucose 5.3 mmol/l

Thyroid function Normal

Aldosterone Normal

Renin Normal

Protein electrophoresis & immunoglobulins Normal

Urinary sodium 94 mmol/l (normal range >20 mmol/L)

Urinary potassium 26.8 mmol/l (normal range >25 mmol/L)

17- hydroxyprogesterone Normal

Short synacthen test (basal) 320 nmol/l

Short synacthen test (30 mins) 750 nmol/l

What is the likely diagnosis?

[Renal tubular acidosis type 18%](#)[Renal tubular acidosis type 27%](#)[Renal tubular acidosis type 458%](#)[Gitelman syndrome8%](#)[Adrenal insufficiency20%](#)

Renal tubular acidosis type 4 is a condition associated with increased urinary ammonia secondary to hypoaldosteronism or pseudohypoaldosteronism. This leads to hyperkalaemia and a hyperchloraemic metabolic acidosis with a normal anion gap.

Both renal tubular acidosis type 1 & 2 lead to low potassium in the context of acidosis.

Gitleman: An autosomal recessive kidney disorder characterized by hypokalemic metabolic alkalosis with hypocalciuria and hypomagnesemia.

Adrenal insufficiency is effectively ruled out with a normal short synacthen test. Candidates would be expected to understand how to perform a short synacthen test and to interpret the results. Laboratory references vary, but in general a basal plasma cortisol should exceed 170 nmol/L and should rise to above 580 nmol/L.

## **Renal tubular acidosis**

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete  $H^+$ ) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

#### Type 2 RTA (proximal)

- decreased  $\text{HCO}_3^-$  reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

#### Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion

- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

#### Question 2 of 207

A 67-year-old man with a history of ischaemic heart disease and type 2 diabetes mellitus is noted to have non-visible haematuria during an annual review. He is currently feeling well and is asymptomatic. The urine dipstick showed blood ++, with no protein and no leucocytes. This result is repeated one week later.

His current medications include aspirin, bisoprolol, atorvastatin, ramipril, metformin and pioglitazone.

Which one of the following drugs should be stopped whilst awaiting further investigations?

[Aspirin19%Ramipril9%Atorvastatin7%Metformin10%Pioglitazone55%](#)

Pioglitazone has been linked to the development of bladder cancer.

### **Thiazolidinediones**

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

#### Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

- Question 2 of 203
- A 25 year old woman presents to the endocrinology clinic. She is concerned because her father had a 'brain tumour' removed 2 years ago and has now been told he has another tumour in his abdomen after going to his doctor with reflux and indigestion. He has been told it might be a genetic problem and is awaiting testing. She is concerned she might also have the condition and so her GP has referred her to the clinic.

She is currently asymptomatic.

On examination there is no abnormality on the cardiovascular, respiratory, abdominal or neurological examinations.

The doctor explain that the most appropriate person to see would be the geneticist to whom her father has been referred. He asks her to obtain the details if her father is willing to provide them and says that he will refer her. In the meaning time he offers to carry out some screening blood tests.

Given the likely underlying diagnosis, which of the following is most likely to be abnormal?

- [Cortisol6%Fasting glucose8%Parathyroid hormone63%Prolactin15%Thyroid stimulating hormone7%](#)

- 

This lady's father is likely to have multiple endocrine neoplasia type 1 (MEN1) as evidenced by 2 MEN1 associated tumours, a pituitary adenoma and a gastrinoma.

Although this lady is asymptomatic, it is important she is offered genetic screening, as the condition is autosomal dominant.

Fasting glucose, parathyroid hormone and prolactin are all biochemical screening tests used for MEN1 associated tumours (insulinoma, parathyroid adenoma and pituitary adenoma respectively). However, hyperparathyroidism is by far the most common initial manifestation and will eventually develop in 90% of MEN1 patients.

ReferencThakker et al. Clinical guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9)2990-3011)

- 

- **Multiple endocrine neoplasia**

- 

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

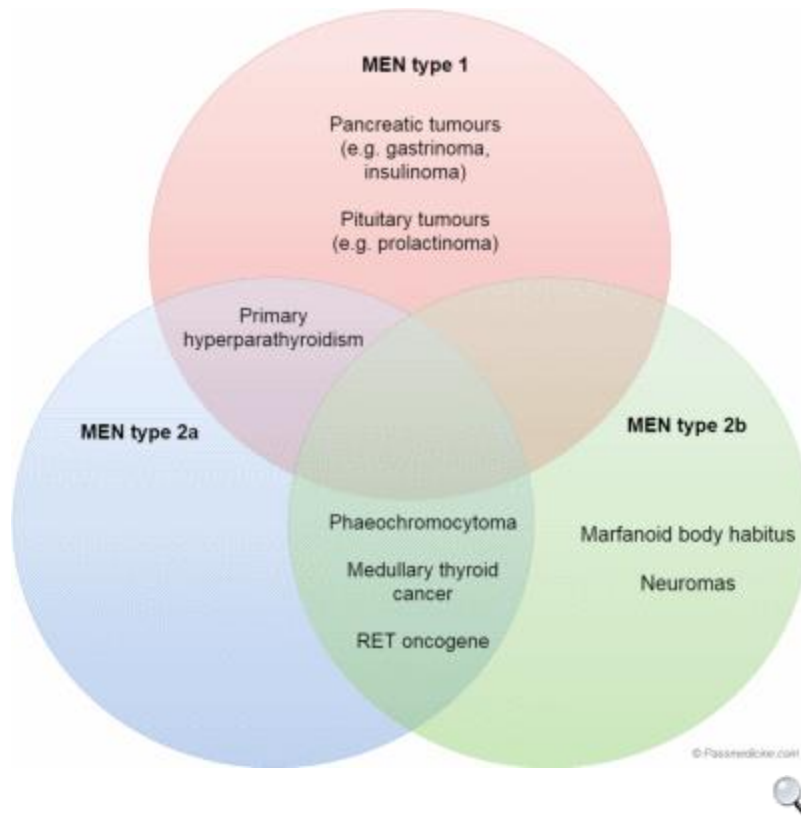
**MEN type I**

**MEN type IIa**

**MEN type IIb**

MEN type I	MEN type IIa	MEN type IIb
3 P's		Medullary thyroid cancer
<b>P</b> arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia	Medullary thyroid cancer (70%)	
<b>P</b> ituitary (70%)	2 P's	1 <b>P</b>
<b>P</b> ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration)	<b>P</b> arathyroid (60%)	<b>P</b> haeochromocytoma
	<b>P</b> haeochromocytoma	Marfanoid body habitus
Also: adrenal and thyroid		Neuromas
MEN1 gene	RET oncogene	RET oncogene
Most common presentation = hypercalcaemia		

- 



- Venn diagram showing the different types of MEN and their associated features

### Question 3 of 203

A 45-year-old woman presents to the Emergency Department with abdominal pain. Her GP is currently investigating her for lethargy, weakness and abdominal pain. Her symptoms have been getting progressively worse over the past few months. There is no past medical history of note.

She smokes 5-10 cigarettes/day and drinks around 20 units of alcohol per week.

A urine dipstick has already been performed: protein trace, blood +, pH 5.5-6.0

Bloods show the following:

Hb	13.6 g/dl	Na <sup>+</sup>	143 mmol/l
Platelets	225 * 10 <sup>9</sup> /l	K <sup>+</sup>	2.3 mmol/l
WBC	8.4 * 10 <sup>9</sup> /l	Urea	6.1 mmol/l
Neuts	6.0 * 10 <sup>9</sup> /l	Creatinine	81 µmol/l
Lymphs	1.9 * 10 <sup>9</sup> /l	Bicarbonate	7 mmol/l
Eosin	0.3 * 10 <sup>9</sup> /l	Chloride	124 mmol/l

An abdominal film is requested due to her recurrent abdominal pains:



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What is the most likely diagnosis?

[Renal tubular acidosis type 1](#) 74% [Renal tubular acidosis type 2](#) 12% [Renal tubular acidosis type 4](#) 6% [Conn's syndrome](#) 5% [Bulimia](#) 4%

Nephrocalcinosis may be caused by renal tubular acidosis **type 1**, hyperparathyroidism and medullary sponge kidney

This is probably a useful 'spot' diagnosis to learn for the exam: nephrocalcinosis on AXR → renal tubular acidosis (RTA) type 1. As well as nephrocalcinosis, the other pointers to RTA type 1 include hypokalaemia and a normal anion gap or hyperchloraemic metabolic acidosis.

If you weren't aware of the link between RTA type 1 and nephrocalcinosis another approach would be to work through the causes of 1. metabolic acidosis and 2. hypokalaemia.

## 1. Metabolic acidosis

It is useful to first calculate the anion gap:

Anion gap = (sodium + potassium) - (bicarbonate + chloride)

= (143 + 2.3) - (7 + 124) = 12.3 mmol/l

A normal anion gap is 8-14 mmol/l

### Causes of a normal anion gap or hyperchloraemic metabolic acidosis

- gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
- renal tubular acidosis
- drugs: e.g. acetazolamide
- ammonium chloride injection
- Addison's disease

### Causes of a raised anion gap metabolic acidosis

- lactate: shock, hypoxia
- ketones: diabetic ketoacidosis, alcohol
- urate: renal failure
- acid poisoning: salicylates, methanol

## 2. Hypokalaemia

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

### Hypokalaemia with alkalosis

- vomiting
- diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

### Hypokalaemia with acidosis

- diarrhoea
- renal tubular acidosis (types 1 and 2)
- acetazolamide

### **Hypokalaemia with alkalosis**

### **Hypokalaemia with acidosis**

- partially treated diabetic ketoacidosis

### **Renal tubular acidosis**

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

#### Type 1 RTA (distal)

- inability to generate acid urine (secrete  $H^+$ ) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



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Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

#### Type 2 RTA (proximal)

- decreased  $\text{HCO}_3^-$  reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

#### Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion

- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

#### Question 4 of 203

A 52 year old lady presents complaining of polydipsia and polyuria. She has a background of hypertension, hypercholesterolaemia and bipolar affective disorder and a strong family history of diabetes - she is unsure which type.

Results show the following:

Na<sup>+</sup> 131mmol/l  
 urine osmolality 287mOsmol/kg (300 - 900mOsmol/kg)  
 plasma osmolality 287mOsmol/kg (285 - 295mOsmol/kg)

Which of the following is the most likely explanation for this lady's symptoms?

[Psychogenic polydipsia61%](#)[Syndrome of inappropriate anti-diuretic hormone \(SIADH\)9%](#)[Diabetes insipidus19%](#)[Diabetes mellitus type 15%](#)[Hyponatraemia5%](#)

Although this lady is biochemically hyponatraemic, this is unlikely to be the cause of her symptoms.

With a past medical history of bipolar affective disorder, although not stated in the question, there is a good chance she may be on lithium which predisposes her to developing nephrogenic diabetes insipidus. However with this diagnosis, we would expect a much lower urine osmolality and a higher plasma osmolality. She would also have a normal to high serum sodium. The opposite would indicate a diagnosis of SIADH (serum hypo-osmolality and high urine osmolality).

The osmolality results here reflect a diagnosis of psychogenic polydipsia with a low urine osmolality and a low end of normal plasma osmolality.

### Hyponatraemia

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood

from a drip arm. Urinary sodium and osmolality levels aid making a diagnosis

### **Urinary sodium > 20 mmol/l**

Sodium depletion, renal loss (patient often hypovolaemic)

- diuretics
- Addison's
- diuretic stage of renal failure

Patient often euvolaemic

- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

### **Urinary sodium < 20 mmol/l**

Sodium depletion, extra-renal loss

- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)

- secondary hyperaldosteronism: heart failure, cirrhosis
- reduced GFR: renal failure
- IV dextrose, psychogenic polydipsia

### **Question 2 of 197**

A 19-year-old girl was seen in clinic with lethargy, weakness worsening over the past 4 weeks. She also complains of recurrent muscle cramps in her legs, causing her to have trouble sleeping. On further questioning she admits to urinary frequency, passing urine up to ten times a day, and feels dehydrated all the time. She also mentions that her periods which were usually irregular, have stopped 4 months ago.

On examination, she is thin, with a body mass index of 17kg/m<sup>2</sup>. Her heart rate is 88 bpm and blood pressure is 108/86 mmHg.

C Reactive protein	2mg/l
Haemoglobin	158 g/l
White cell count	7.6 x 10 <sup>9</sup> /L
Na+	136 mmol/l
K+	2.9 mmol/l
Urea	7.2 mmol/l
Creatinine	108 µmol/l
Corrected calcium	2.42 mmol/l

Venous blood gas result

pH	7.532
Bicarbonate	37mmol/l

What would be the next most useful investigation?

[Transvaginal ultrasound \(TVUS\) of the ovaries](#)5% [Urine diuretic assay](#)44% [Early morning cortisol](#)13% [Serum renin and aldosterone levels](#)30% [Fasting blood glucose levels](#)7%

Patients with hypokalaemia, metabolic alkalosis and a normal - low blood pressure the following differentials should be considered - diuretic abuse, Bartter's syndrome, Gitelman's syndrome. Of the three, the most common cause is diuretic abuse, especially in young women, and can be ruled out with a urine diuretic assay.

Bartter's syndrome presents early in life, with classical features of triangular facies, polyuria, polydipsia and renal failure. Serum renin and aldosterone levels are high despite a low or normal blood pressure. Urine calcium may be raised, and renal stones are a common feature. In Gitelman's syndrome patients may present later on in adulthood, but have a milder disease course or may be asymptomatic compared to patients with Bartter's syndrome. Hypomagnesaemia and hypocalciuria differentiates Gitelman's syndrome from Bartter's syndrome.

This patient may need other further investigations such as a TVUS, early morning cortisol and fasting blood glucose tests to rule out other conditions, but in view of her biochemistry profile, a urine diuretic assay would be the most useful next investigation to perform.

## Hypokalaemia

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

### Hypokalaemia with alkalosis

- vomiting
- diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

### Hypokalaemia with acidosis

- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

### Question 5 of 197

A 41-year-old woman is admitted to hospital with acute epigastric abdominal pain that radiates to her back. She has nausea but has not vomited. A diagnosis of acute pancreatitis is suspected and she is commenced on intravenous fluids. Her observations include a blood pressure of 129/72 mmHg, pulse of 88 bpm, and oxygen sats of 97%.

Blood tests are performed and reveal:

Hb	13.9 g/l
Platelets	$194 \times 10^9/l$
WBC	$8.6 \times 10^9/l$
Na <sup>+</sup>	139 mmol/l
K <sup>+</sup>	4.2 mmol/l
Urea	4.1 mmol/l
Creatinine	92 $\mu$ mol/l
Bilirubin	10 $\mu$ mol/l
ALP	39 u/l
ALT	34 u/l
$\gamma$ GT	44 u/l
Albumin	48 g/l

Triglycerides 12.1 mmol/l  
HDL cholesterol 1.1 mmol/l  
LDL cholesterol 3.5 mmol/l

What is the most appropriate treatment for this patient's condition?

[Atorvastatin 15% Fenofibrate 60% Lovastatin 3% Ezetimibe 17% Alirocumab 5%](#)

The diagnosis is hypertriglyceridaemia, which has caused this patient's acute pancreatitis. Fibrates are the treatment for hypertriglyceridaemia at high enough levels to cause acute pancreatitis.

### **Primary hypertriglyceridaemia**

Usually due to polygenic factors

May also be due to lipoprotein lipase deficiency

Management

- fibrates are generally used first-line
- statins do reduce triglyceride levels and they may be indicated, particularly if there is mixed hyperlipidaemia

### **Question 2 of 192**

A 16-year-old male presents with 3 months of chronic headaches and visual blurring. He has no past medical history and no known family history. On examination, his heart sounds are normal with no added sounds and the respiratory examination is unremarkable. He has no focal neurological signs. Fundoscopy reveals papilloedema, hard exudates and flame haemorrhage. His blood pressure is 226/160 mmHg. His blood tests and arterial blood gas are as follows:

Na<sup>+</sup> 145 mmol/l  
K<sup>+</sup> 2.9 mmol/l  
Urea 5.4 mmol/l  
Creatinine 72 µmol/l



pH 7.49  
PaO<sub>2</sub> 13kPa  
PaCO<sub>2</sub> 3.4 kPa  
Bicarbonate 34 mmol/L

Serum ambulatory renin activity 0.2 pmol/L @ 3-4 hours (normal range 0.8-3.5 pmol/ml/hr)  
Serum ambulatory aldosterone 24 pmol/L @ 3-4 hours (normal range 100-800)

What is the optimal long-term treatment?

[Amlodipine7%Ramipril12%Atenolol5%Doxazosin11%Amiloride65%](#)

The patient is young and presents with grade 4 hypertensive retinopathic changes associated with a systolic of over 200mmHg, associated with hypokalaemia and a metabolic alkalosis. Importantly, both renin and aldosterone are decreased, ruling out primary hyperaldosteronism. The diagnosis is thus likely to be Liddle's syndrome, a genetic disorder of ENaC channels in the collecting duct, leading to increased sodium reabsorption and increased potassium excretion. The treatment is with amiloride, a potassium sparing diuretic that directly blocks collecting tubule sodium channels and resolves hypertension.

### **Liddle's syndrome**

Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

Treatment is with either amiloride or triamterene

### **Question 3 of 192**

A 45-year-old female presents with a 2-year history of headache and visual blurring. When initially presenting to her GP 2 years ago her blood pressure was found to be 235/160mmHg. Subsequently, despite maximal doses of four anti-hypertensives, including 50mg spironolactone, her blood pressure remains poorly controlled. Her latest blood tests demonstrate the following:

Na<sup>+</sup> 140 mmol/l  
K<sup>+</sup> 2.9 mmol/l  
Urea 5.8 mmol/l  
Creatinine 78 µmol/l  
CRP 2 mg/l

Serum ambulatory renin activity 0.34 pmol/L @ 3-4 hours (normal range 0.8-3.5 pmol/ml/hr)

Serum ambulatory aldosterone 2052 pmol/L @ 3-4 hours (normal range 100-800)

A CT adrenal reveals a right adrenal mass of 2.5cm diameter. The patient is keen to take away the underlying problem. What is the most appropriate next management step?

[Add amiloride9%](#)[Add eplerenone8%](#)[Increase spironolactone to 100mg OD7%](#)[Adrenal vein sampling33%](#)[Right adrenalectomy43%](#)

The patient presents with poorly controlled hypertension, is hypokalaemic, hypertensive, metabolically alkalotic, has increased aldosterone and reduced renin. The underlying diagnosis is Conn's disease. The treatment involves removal of the aldosterone secreting tumour. However, those pursuing adrenalectomy must undergo adrenal vein sampling first, CT imaging alone is not diagnostic of the symptomatic side responsible for aldosterone secretion.

## Primary hyperaldosteronism

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the cause in up to 70% of cases. Differentiating between the two is important as this determines treatment. Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism

### Features

- hypertension
- hypokalaemia (e.g. muscle weakness)
- alkalosis

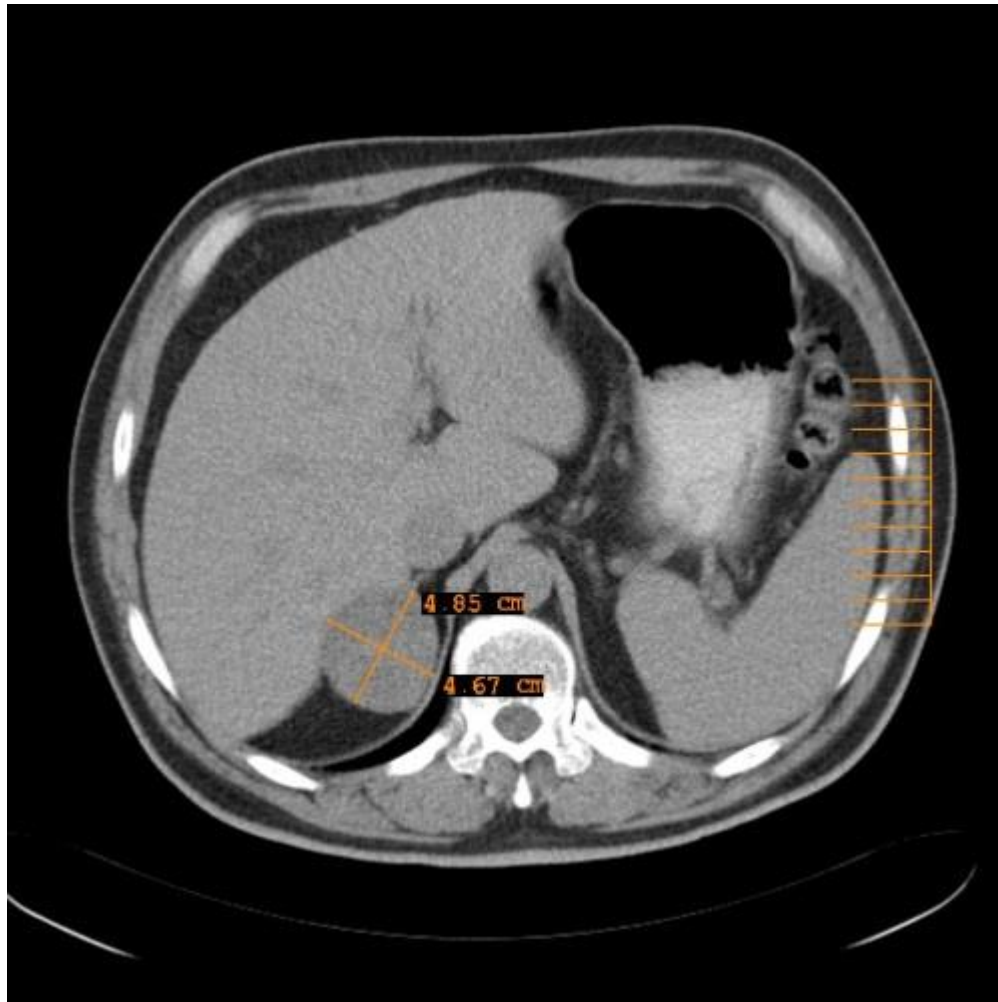
### Investigations

- high serum aldosterone
- low serum renin

- high-resolution CT abdomen
- adrenal vein sampling

### Management

- adrenal adenoma: surgery
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



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CT abdomen showing a right-sided adrenal adenoma in a patient who presented with hypertension and hypokalaemia. The adenoma can be seen 'next to' or 'below' the liver.

A 28-year-old lady is diagnosed with gestational diabetes in her first pregnancy. Her fasting blood glucose is 5.9mmol/l and blood glucose after oral glucose tolerance test (OGTT) is 8.2mmol/l. Blood glucose control during pregnancy is achieved with diet, exercise and metformin. She gives birth to a healthy child at 39 weeks. A fasting blood glucose at day 1 postpartum is 5.2mmol/l.

Which of the following statements is correct with respect to follow-up monitoring for diabetes?

[OGTT 6-13 weeks postpartum33%](#)[Fasting blood glucose test 6-13 weeks postpartum36%](#)[No routine follow up unless further pregnancy13%](#)[HbA1c 6-13 weeks postpartum9%](#)[Annual fasting blood glucose checks only8%](#)

Women with gestational diabetes whose glucose returns to normal after birth need a postnatal glucose check 6-13 weeks postpartum to stratify their risk of developing diabetes in the future. NICE recommends that this is a fasting blood glucose. Further follow up will depend on the result of this postnatal check. Even if postnatal glucose is less than 6mmol/l, annual fasting glucose checks are still recommended thereafter.

## **Pregnancy: diabetes mellitus**

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates around 1 in 40 pregnancies. NICE updated the guidance in 2015

Risk factors for gestational diabetes

- BMI of  $> 30 \text{ kg/m}^2$
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- women who've previously had gestational diabetes: oral glucose tolerance test (OGTT) should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

## Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is  $\geq 5.6$  mmol/l
- 2-hour glucose is  $\geq 7.8$  mmol/l

## Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about selfmonitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is  $< 7$  mmol/l a trial of diet and exercise should be offered
- if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
- if glucose targets are still not met insulin should be added to diet/exercise/metformin
- if at the time of diagnosis the fasting glucose level is  $\geq 7$  mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

## Management of pre-existing diabetes

- weight loss for women with BMI of  $> 27$  kg/m<sup>2</sup>
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

## Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

### Question 3 of 189

A 80-year-old patient was referred to Accident and Emergency after being found unresponsive in his home. He had just completed a course of antibiotics for a chest infection. He had not been seen for the preceding 36 hours. He had a past medical history of hypertension and type two diabetes.

His medication included Metformin, Gliclazide, Humulin M3 insulin twice a day, Ramipril and Bendroflumethiazide.

His initial examination revealed. Blood pressure 104/53, heart rate 103 beats per minute, respiratory rate 24 and oxygen saturations 90% on air. He had inspiratory crackles on his left lower lung zone. He had sunken eyes, capillary refill time of four seconds and no lower limb swelling. GCS 13 out of 15.

Initial blood tests;

Hb	11.0 g/dL
WCC	$21.4 \times 10^9/l$
Platelets	$189 \times 10^9/l$
CRP	340 mg/L
Na+	149 mmol/l
K+	4.4mmol/l
Ur	28 mmol/l
Cr	180 $\mu$ mol/l
Glucose	54mmol/l

ABG on air

pH	7.32
pCO2	3.7kPa
pO2	9kPa
HCO3	18 mmol/l
Lactate	2.4mmol/l

Urine dipstick analysis - ++ glucose, - WCC, - leucocytes, + ketones

The patient was treated with oxygen, intravenous antibiotics for a chest infection and prophylactic low molecular weight heparin. They were treated with the local diabetic ketoacidosis protocol with IV insulin sliding scale and IV fluids 5500ml in 24 hours.

His repeat bloods 12 hours later were;

Na+ 132 mmol/l  
K+ 3.9 mmol/l  
Ur 12 mmol/l  
Cr 110  $\mu$ mol/l  
Glucose 5 mmol/l  
HCO<sub>3</sub> 24 mmol/l  
Lactate 1.7 mmol/l  
CRP 270mg/l

The patient developed a grand mal seizure. His Glasgow coma scale remained 10 an hour after the seizure.

What is the most likely cause of his neurological deterioration?

[Hypoglycaemia6% Intracranial venous sinus thrombosis4% Cerebral oedema82% Sepsis5% Renal failure3%](#)

All the answers are potentially associated with hyperosmolar hyperglycaemic coma. The current guidance advises treatment initially with normal saline intravenous rehydration. The target reduction in osmolality is 3-8 mosmol/kg an hour. Only if this target is not being met and the glucose level not reducing sufficiently is insulin to be started.

This patient developed cerebral oedema secondary to rapid reduction in serum osmolality.

## **Hyperosmolar hyperglycaemic state**

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality >320mosmol/kg
- Hyperglycaemia >30 mmol/L with pH >7.3, bicarbonate >15mmol/L and no significant ketonenaemia <3mmol/L

Question 6 of 189

A 67-year-old Caucasian man presents with progressive deafness and difficulty chewing. He also states that his father and paternal uncles suffered from similar symptoms that required

medication. On examination, it is noted that there is frontal bossing. Further investigations find an elevated alkaline phosphatase and a serum calcium at the upper end of the normal range. His other investigations are normal. What is the best first line treatment for this man?

[Calcium supplementation4%Bisphosphonates67%Calcium and Vitamin D supplementation8%Calcitonin12%Surgery9%](#)

This gentleman has findings consistent with Paget's disease of the bone given his clinical symptoms, ethnic background, family history and biochemical results. The NICE guidelines recommend bisphosphonates as first line treatment in symptomatic patients. In asymptomatic patients, watchful waiting may be sufficient initially.

Supplementation is insufficient in this patient given that he is symptomatic. Calcitonin is used when there is hypocalcaemia and taking bisphosphonates may lower levels further. Surgery may be required if there are complications such as fractures or severe osteoarthritis but not at this stage.

### **Paget's disease of the bone**

Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium\* and phosphate are typically normal
- skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's



- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

### Complications

- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



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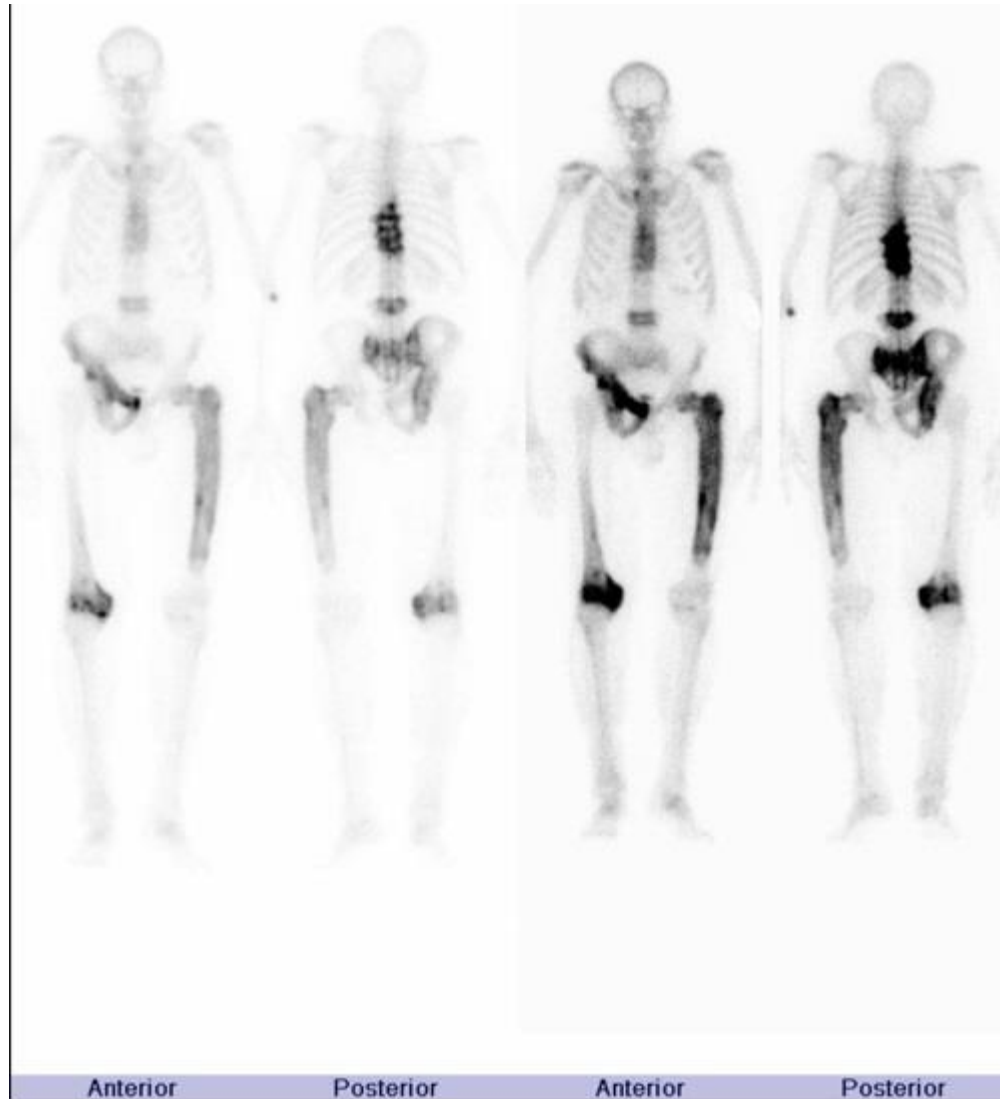
The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.



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Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.



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Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilization

#### Question 7 of 189

A 38-year-old lady presents to clinic with her 69-year-old mother for a follow-up appointment. The mother had presented 3 months previously under the acute medical take with headaches, sweating, abdominal pain and wild fluctuations in blood pressure. She is currently being followed up by the appropriate surgical team and her symptoms are currently well controlled with medical treatments. On examination today, you note a lump in her anterior neck and you are given the following blood tests:

Calcium (corrected) 3.68 mmol/l  
 Phosphate 0.38 mmol/l  
 Vitamin D3 115 nmol/l (75-200 nmol/l)  
 Parathyroid hormone 19 pmol/l (0.8 - 8.5 pmol/l)

You have referred the patient to endocrine surgeons for neck biopsies and urgent review. The daughter is concerned she may have the same symptoms later in life. What should you offer the daughter?

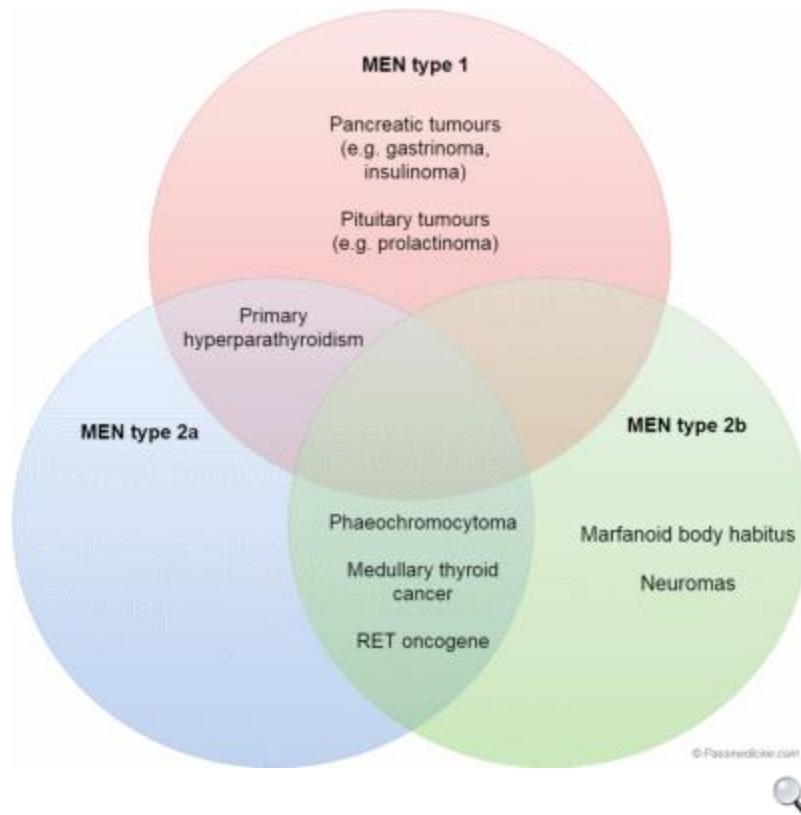
[Reassurance14%](#)[Genetic testing for patient and daughter60%](#)[Offer annual follow up for surveillance9%](#)[CT abdomen/pelvis with contrast5%](#)[Serum bone and calcium homeostasis profile12%](#)

The patient describes features consistent with pheochromocytoma, the appropriate surgical team would be endocrine surgery, who would arrange for a resection. The new blood tests are suggestive of primary hyperparathyroidism, the neck lumps possible medullary thyroid tumour, resulting in a unifying diagnosis of MEN 2a. The daughter can undergo genetic testing for RET-mutation.

## Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	MEN type IIa	MEN type IIb
3 P's		Medullary thyroid cancer
<b>P</b> arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia	Medullary thyroid cancer (70%)	
<b>P</b> ituitary (70%)	2 P's	1 <b>P</b>
<b>P</b> ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration)	<b>P</b> arathyroid (60%)	<b>P</b> heochromocytoma
	<b>P</b> heochromocytoma	Marfanoid body habitus
Also: adrenal and thyroid		Neuromas
MEN1 gene	RET oncogene	RET oncogene
Most common presentation = hypercalcaemia		



Venn diagram showing the different types of MEN and their associated features

#### Question 1 of 182

A 19-year-old man is reviewed prior to discharge. He presented with vomiting and abdominal pain and was found to have diabetic ketoacidosis. He was managed as an inpatient for five days before being well enough for discharge. He is also diagnosed with type 1 diabetes mellitus on this admission as a cause of the diabetic ketoacidosis. He has been educated by the diabetic nurse on how to manage his diabetes and insulin at home, but he is concerned about what his target plasma glucose should be after eating.

What is the recommended target after eating to be achieved by home monitoring?

[3-6mmol/litre6%5-10mmol/litre20%5-9mmol/litre44%7-12mmol/litre27%2-9 mmol/litre3%](#)

The correct answer is 5-9mmol/litre. NICE recommends that people with type 1 diabetes should aim for 5-7mmol/litre on waking, 4-7mmol/litre before meals and 5-9mmol/litre 90 minutes after eating. Frequent testing is very important in patients starting with insulin therapy to avoid both high and low sugar levels.

Source:

'Type 1 diabetes in adults: diagnosis and management' Clinical guideline [NG17]. The National Institute for Health and Care Excellence, August 2015.

## Insulin therapy

Insulin therapy revolutionised the management of diabetes mellitus when it was developed in the 1920's. It is still the only available treatment for type 1 diabetes mellitus (T1DM) and is widely used in type 2 diabetes mellitus (T2DM) where oral hypoglycaemic agents fail to gain adequate control.

It can sometimes seem daunting to understand the various types of insulin but it is important you have a basic grasp to avoid potential harm to patients.

### Classification of insulin

By manufacturing process

- porcine: extracted and purified from pig pancreas
- human sequence insulin: either produced by enzyme modification of porcine insulin (emp) or biosynthetically by recombinant DNA using bacteria (crb, prb) or yeast (pyr)
- analogues

By duration of action

	Onset	Peak	Duration
<b>Rapid-acting insulin analogues</b>	5 mins	1 hour	3-5 hours
<b>Short-acting insulin</b>	30 mins	3 hours	6-8 hours
<b>Intermediate-acting insulin</b>	2 hours	5-8 hours	12-18 hours
<b>Long-acting insulin analogues</b>	1-2 hours	Flat profile	Up to 24 hours
<b>Premixed preparations</b>	-	-	-

Patients often require a mixture of preparations (e.g. both short and long acting) to ensure stable glycaemic control throughout the day.

Rapid-acting insulin analogues

- the rapid-acting human insulin analogues act faster and have a shorter duration of action than soluble insulin (see below)
- may be used as the bolus dose in 'basal-bolus' regimes (rapid/short-acting 'bolus' insulin before meals with intermediate/long-acting 'basal' insulin once or twice daily)
- insulin aspart: NovoRapid
- insulin lispro: Humalog

### Short-acting insulins

- soluble insulin examples: Actrapid (human, pyr), Humulin S (human, prb)
- may be used as the bolus dose in 'basal-bolus' regimes

### Intermediate-acting insulins

- isophane insulin
- many patients use isophane insulin in a premixed formulation with

### Long-acting insulins

- insulin detemir (Levemir): given once or twice daily
- insulin glargine (Lantus): given once daily

### Premixed preparations

- combine intermediate acting insulin with either a rapid-acting insulin analogue or soluble insulin
- Novomix 30: 30% insulin aspart (rapid-acting), 70% insulin aspart protamine (intermediate-acting)
- Humalog Mix25: 25% insulin lispro (rapid-acting), 75% insulin lispro protamine (intermediate-acting); Humalog Mix50: 50% insulin lispro, 50% insulin lispro protamine
- Humulin M3: biphasic isophane insulin (human, prb) - 30% soluble (short-acting), 70% isophane (intermediate-acting)
- Insuman Comb 15: biphasic isophane insulin (human, prb) - 30% soluble (short-acting), 70% isophane (intermediate-acting)

### **Administration of insulin**

The vast majority of patients administer insulin subcutaneously. It is important to rotate injection sites to prevent lipodystrophy. Insulin pumps are available ('continuous subcutaneous insulin infusions') which delivers a continuous basal infusion and a patient-activated bolus dose at meal times.

Intravenous insulin is used for patients who are acutely unwell, for example with diabetic ketoacidosis. Inhaled insulin is available but not widely used and oral insulin analogues are in development but have considerable technical hurdles to clear.

### Question 3 of 182

A 23-year-old Malaysian man presented to the emergency department with sudden onset right arm weakness that came on earlier in the morning after waking up. He denies any slurring of his speech. He has had one previous episode a month ago but that episode involved mild right leg weakness which resolved after 30 minutes, this time he is anxious as he was unable to move his arm and it has not resolved after 2 hours. His past medical history includes Grave's disease, and he takes carbimazole 20mg twice daily, however, he admits he has not been taking his carbimazole for the past week as he just returned from a month long holiday and had run out of medication.

On examination his temperature was 37.5°C, heart rate was 84 bpm, blood pressure was 114/68 mmHg, respiratory rate was 18 breaths per minute, and oxygen saturation was 98% on air. There was a fine tremor in both hands. Neurological examination revealed flaccid paralysis of the right arm, affecting the extensor muscles more than the flexor muscles (power 2/5 in the shoulder extensors). Reflexes and sensation to soft touch were normal. There was no disturbance of speech or facial asymmetry. There was a palpable smooth thyroid goitre in the midline of the neck.

C Reactive protein	6 mg/l
Haemoglobin	156 g/l
White cell count	$6.6 \times 10^9/L$
Na+	145 mmol/l
K+	3.1 mmol/l
Urea	5.2 mmol/l
Creatinine	78 $\mu$ mol/l
Corrected calcium	2.42 mmol/l
Thyroid stimulating hormone (TSH)	<0.03 $\mu$ U/ml (Reference range 0.3 - 4.0 $\mu$ U/ml)
Free T4	3.14 ng/dL (Reference range 0.7 - 1.4ng/dL)
Free T3	1.44ng/dL (Reference range 0.2 - 0.5ng/dL)

What is the next most appropriate management step?

[Computer Tomography scan \(CT\) of the head](#)24%[Hydrocortisone](#)21%[Fludrocortisone](#)6%[Carbimazole](#)13%[Intravenous potassium chloride](#)36%



This patient has thyrotoxic periodic paralysis, a rare condition associated with hyperthyroidism. It is more common in males of oriental descent and presents between the second to third decade of life. There is an association with the HLA-DRw8 genotype. It is characterised by recurrent episodes of proximal muscle weakness and can vary from mild weakness to quadriplegia. Bulbar, respiratory muscles and cranial nerves are rarely affected.

Patients are hypokalaemic during attacks as thyrotoxicosis leads to an intracellular potassium shift, which resolves when potassium returns to the extracellular space. Patients may also have hypophosphataemia and hypomagnesaemia.

Treatment for acute attacks is potassium replacement, but patients should be monitored closely for hyperkalaemia. Definitive management includes the management of thyrotoxicosis with pharmacological, surgical or radioactive iodine management.

### **Hypokalaemic periodic paralysis**

Hypokalaemic periodic paralysis is a rare autosomal dominant disorder characterised by episodes of paralysis, typically occur at night. The underlying defect is a mutation in muscle voltage-gated calcium channels. Attacks may be precipitated by carbohydrate meals

#### **Management**

- lifelong potassium supplementation

#### **Question 4 of 182**

A 72-year-old woman is recovering on the neurosurgical unit following a subdural haemorrhage. Four days earlier she underwent Burr hole surgery. You are asked to see her due to a persistently low sodium for the past three days. You note the following investigations:

Day 2 post-surgery

Serum Na<sup>+</sup> 116 mmol/l

Day 3 post-surgery

Serum Na<sup>+</sup> 117 mmol/l

Day 4 post-surgery

Serum Na<sup>+</sup> 115 mmol/l

Urinary Na<sup>+</sup> 25 mmol/l

Serum osmolality 280 mmol/l

Examination of the patient demonstrates dry mucous membranes and delayed capillary refill time.

What is the most likely diagnosis?

[SIADH 34% Diabetes insipidus 15% Cerebral salt wasting syndrome 41% Renal tubular acidosis type IV 4% Sheehan's syndrome 6%](#)

Diabetes insipidus is classically associated with hypernatraemia. Sheehan's syndrome refers to the specific situation of pituitary necrosis following childbirth. The cardinal feature of renal tubular acidosis type IV is hyperkalaemia.

This leaves SIADH and cerebral salt wasting syndrome. The hydration status in this patient can be considered hypovolaemic making SIADH unlikely (typically euvolaemic). Additionally, this diagnosis should only be made in the absence of hypothyroidism and adrenal dysfunction.

Cerebral salt wasting syndrome can occur following neurosurgery. It occurs due to sodium wasting in the urine. Comparatively, it is treated with replacing fluid and sodium losses.

## **Hyponatraemia**

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolality levels aid making a diagnosis

### **Urinary sodium > 20 mmol/l**

Sodium depletion, renal loss (patient often hypovolaemic)

- diuretics
- Addison's
- diuretic stage of renal failure

Patient often euvolaemic

- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

### **Urinary sodium < 20 mmol/l**

Sodium depletion, extra-renal loss

- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)

- secondary hyperaldosteronism: heart failure, cirrhosis
- reduced GFR: renal failure
- IV dextrose, psychogenic polydipsia

### Question 5 of 182

A 17-year-old girl is brought into the emergency department by her mother. The patient appears terrified after she experienced an episode on waking earlier in the morning when she could not move at all for 2 hours. This was her second episode. She reports no loss of consciousness and was aware throughout the episode. She has no other past medical history documented. She is not aware of a previous episode of epilepsy. On examination, her heart sounds and breath sounds are unremarkable. Neurological examination demonstrated no abnormalities. She has normal dentition and her body mass index is 19.5 kg/m<sup>2</sup>. A 12 lead ECG demonstrated a jerky baseline with flat T waves. What is the most likely diagnosis?

[Partial or absence seizures10% Guillain-Barre syndrome3% Botulinum toxicity5% Myasthenia gravis4% Hypokalaemia78%](#)

The patient describes episodes of periodic paralysis and the ECG characteristics are consistent with that of hypokalaemia. The underlying diagnosis is a rare familial condition of skeletal muscle ion channels called hypokalaemic periodic paralysis, which tends to develop in childhood and adolescence. Attacks last hours and the neurological examination is usually unremarkable in between attacks. The average potassium on diagnosis is 2.4 mmol/L<sup>1</sup>. Diagnosis is often made clinically in association with low potassium but genetic testing can help if known mutations are present.

1. Miller TM, Dias da Silva MR, Miller HA et al. Correlating phenotype and genotype in the periodic paralyses. *Neurology*. 2004;63(9):1647.

## **Hypokalaemic periodic paralysis**

Hypokalaemic periodic paralysis is a rare autosomal dominant disorder characterised by episodes of paralysis, typically occur at night. The underlying defect is a mutation in muscle voltage-gated calcium channels. Attacks may be precipitated by carbohydrate meals

### **Management**

- lifelong potassium supplementation

### **Question 6 of 182**

A frail 82-year-old gentleman was brought in by his daughter, who found him on the floor in his flat. He had tripped in a mechanical and had been unable to get back up, lying on the floor for the past 3 days. On examination, he appears extremely dehydrated but has no specific focal weakness, systemic examination is unremarkable. He has sustained no musculoskeletal injuries. His blood tests are as follows:

Na <sup>+</sup>	168 mmol/l
K <sup>+</sup>	6.0 mmol/l
Urea	24 mmol/l
Creatinine	260 µmol/l (baseline 107 three months ago)
Creatinine kinase	11,000 mmol/l

ECG shows normal sinus rhythm at 99/ minute.

You diagnose him with rhabdomyolysis and an acute kidney injury, likely of a pre-renal cause. Intravenous fluid rehydration is initiated with intravenous 5% dextrose. You ask your colleague to check the patient's blood tests in 12 hours.

What is the aim of correcting the patient's hypernatraemia?

Reduce blood sodium to under 145 mmol/l as quickly as possible<sup>3%</sup>Reduce blood sodium by 0.5mmol/hr. The drop in 12 hours should be no greater than 6 mmol/l<sup>62%</sup>Reduce blood sodium by 1mmol/hr. The drop in 12 hours should be no greater than 12 mmol/l<sup>22%</sup>Aim for blood sodium above 145 mmol/l<sup>3%</sup>Blood sodium does not require monitoring if intravenous fluids is running, CK falling and renal function improving<sup>9%</sup>

## Hypernatraemia

### Causes of hypernatraemia

- dehydration
- osmotic diuresis e.g. hyperosmolar non-ketotic diabetic coma
- diabetes insipidus
- excess IV saline

Hypernatraemia should be corrected with great caution. Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death<sup>1</sup>. Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate<sup>1</sup>.

1. Reynolds RM, Padfield PL, Seckl JR; Disorders of sodium balance. BMJ. 2006 Mar 25;332(7543):702-5.

### Question 7 of 182

A 40-year-old man is referred for difficult to control hypertension. This was diagnosed three years ago and has not responded to a combination of ramipril, indapamide and amlodipine. On examination his blood pressure today is 168/110 mmHg despite his regular medication. His most recent blood tests show the following:

Na <sup>+</sup>	140 mmol/l
K <sup>+</sup>	2.9 mmol/l
Urea	5.5 mmol/l

Creatinine 86  $\mu\text{mol/l}$

A CT abdomen is requested:



© Image used on license from [Radiopaedia](#)

What is the most likely diagnosis?

[Adrenal adenoma](#)56%[Pheochromocytoma](#)13%[Adrenal hyperplasia](#)18%[Coarctation of the aorta](#)4%[Renal artery stenosis](#)8%

The combination of hypertension and hypokalaemia is strongly suggestive of primary hyperaldosteronism. The CT scan shows a large unilateral adenoma, helping to differentiate between Conn's syndrome (adrenal adenoma) and adrenal hyperplasia.

## **Primary hyperaldosteronism**

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the cause in up to 70% of cases. Differentiating between the two is important as this determines treatment. Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism

### **Features**

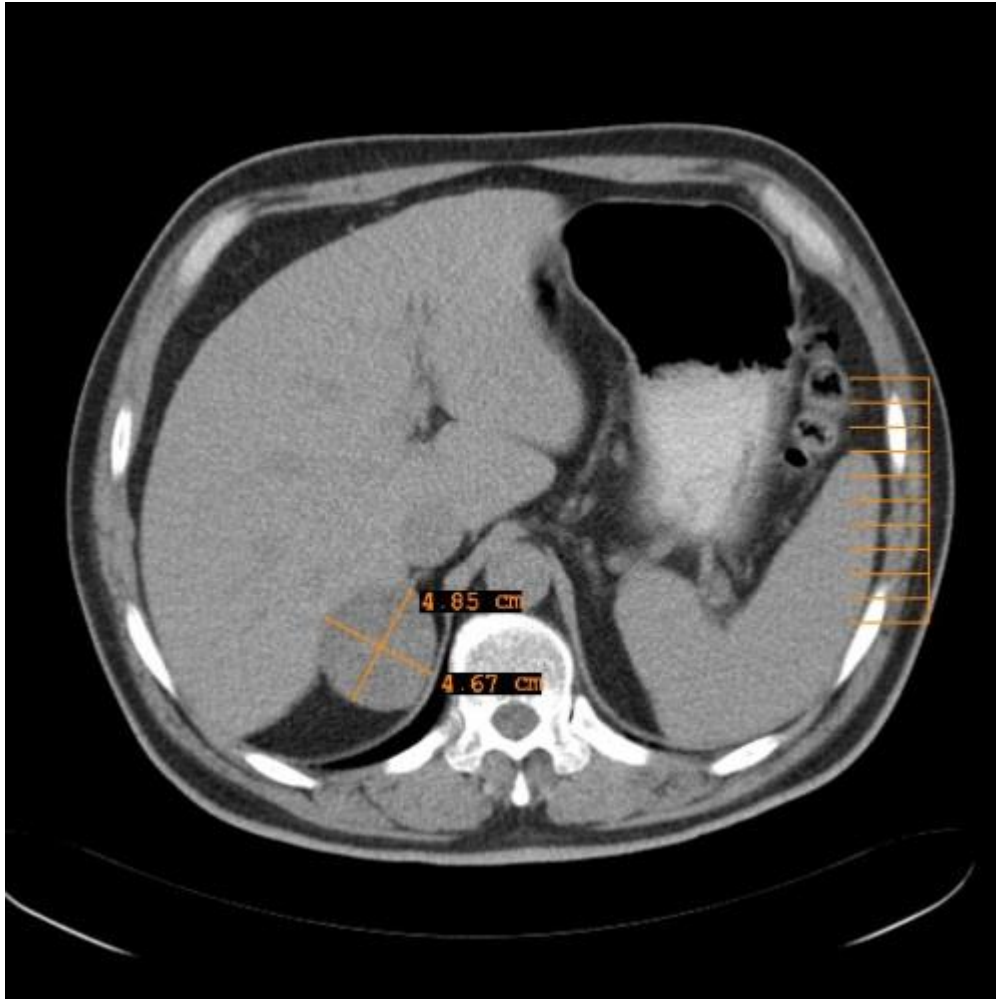
- hypertension
- hypokalaemia (e.g. muscle weakness)
- alkalosis

### **Investigations**

- high serum aldosterone
- low serum renin
- high-resolution CT abdomen
- adrenal vein sampling

### **Management**

- adrenal adenoma: surgery
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

CT abdomen showing a right-sided adrenal adenoma in a patient who presented with hypertension and hypokalaemia. The adenoma can be seen 'next to' or 'below' the liver.

#### Question 8 of 182

A 46-year-old woman with adenocarcinoma of the breast with liver metastases presents to the emergency department with increased thirst and abdominal pain.

She is dehydrated on examination, with a left-sided mastectomy scar and an enlarged liver with an irregular edge. Heart rate is 95bpm, respiratory rate is 18/min, she is afebrile and her oxygen saturation's are 99% on air.

Bloods:

Hb 105 g/l Na<sup>+</sup> 135 mmol/l Bilirubin 40 µmol/l



Platelets	350 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.7 mmol/l	ALP	150 u/l
WBC	9 * 10 <sup>9</sup> /l	Urea	7.9 mmol/l	ALT	140 u/l
Neuts	4.0 * 10 <sup>9</sup> /l	Creatinine	150 µmol/l	γGT	250 u/l
Lymphs	3. * 10 <sup>9</sup> /l			Albumin	24 g/l
Eosin	0.1 * 10 <sup>9</sup> /l	Ca (adj)	3.45mmol/l	PTH	2ng/dl

What is the most appropriate first step in her management?

[Refer to oncology for urgent chemotherapy6%Furosemide5% Intravenous fluid74%IV bisphosphonate9%Prednisolone6%](#)

IV fluid therapy is the first-line management in patients with hypercalcaemia. The management of hypercalcaemia of malignancy hinges around rapid intravenous fluid resuscitation. A large volume should be given over a short period of time.

This patient should be discussed with the oncology team, but there is not an indication for emergency chemotherapy.

Furosemide is an adjunct to the management of hypercalcaemia and might be considered, should the initial fluid resuscitation be ineffective. Similarly, hypercalcaemia of malignancy can be treated with IV bisphosphonates.

Steroids are indicated in hypercalcaemia secondary to sarcoidosis.

## **Hypercalcaemia: management**

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days.

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

Loop diuretics such as furosemide are sometimes used in hypercalcaemia, particularly in patients who cannot tolerate aggressive fluid rehydration. However, they should be used with caution as they may worsen electrolyte derangement and volume depletion.

]

#### Question 1 of 174

A 29-year-old woman is referred to the Endocrinology clinic as she has just found out she is pregnant. She was diagnosed with hypothyroidism three years ago and is currently stable on a dose of levothyroxine 75mcg od. She has also been taking folic acid 400mcg od for the past 6 months. Her last bloods taken 6 months ago show the following:

TSH 1.4 mU/l

You request a repeat TSH and free T4 measurement. What is the most appropriate next step?

[Decrease levothyroxine to 50mcg od](#)6% [Keep levothyroxine at 75mcg od](#)13% [Increase levothyroxine to 100mcg od](#)55% [Keep levothyroxine at 75mcg od + increase folic acid to 5mg od](#)22% [Stop levothyroxine until TSH known](#)4%

Female with hypothyroidism → immediately increase levothyroxine and monitor TSH closely

### **Hypothyroidism: management**

#### Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'\* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value
- there is no evidence to support combination therapy with levothyroxine and liothyronine

#### Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

#### Interactions

- iron: absorption of levothyroxine reduced, give at least 2 hours apart

\*source: NICE Clinical Knowledge Summaries

#### Question 2 of 174

You are asked to review a 67-year-old man who is currently an inpatient on a surgical ward with new paraesthesia in his fingers. He was admitted for an elective parathyroidectomy three days ago for fairly long standing hyperparathyroidism and subsequent hypercalcaemia. He had a single parathyroid adenoma excised which had been identified on pre-operative MIBI scanning. The procedure was without complications but he is now complaining of a tingling sensation in his fingers that he first noticed about twelve hours ago. He also complains of new severe pain in both of his ankles which is worse when he walks, but also present at rest. The surgical SHO has already arranged x-rays of the patient's ankles and these reveal multiple osteolytic lesions which have been reported as being suspicious for metastatic disease. He is otherwise fit and well and his only regular medications are paracetamol, tramadol and prophylactic dalteparin. His blood tests are as follows.

Adjusted Calcium 1.84 mmol/L

Magnesium 0.7 mmol/L

What is the most likely explanation for his current symptoms?

[Metastatic parathyroid cancer7%Secondary hyperparathyroidism8%Hypomagnesaemia11%Hungry bone syndrome57%Secondary hypoparathyroidism17%](#)

Hypocalcaemia after parathyroid surgery is relatively common and usually 'benign' and associated with a transient hypoparathyroidism. However, it can sometimes be more marked and give rise to symptoms such as perioral or finger paraesthesia. This state alone would not, however, explain his ankle pain or x-ray findings.

Although hypomagnesaemia may also be present and should be treated, it does not explain the symptoms. Metastatic parathyroid cancer is a possibility given the x-ray findings, but is very

uncommon and is less likely given that his hyperparathyroidism and hypercalcaemia was long standing (i.e. indolent). Secondary hyperparathyroidism is the syndrome of appropriately raised parathyroid hormone in response to hypocalcaemia, usually secondary to chronic kidney disease. Secondary hypoparathyroidism describes the normal parathyroid hormone suppression that occurs in hypercalcaemia secondary to non-parathyroid causes, such as malignancy.

## **Hungry bone syndrome**

Hungry bone syndrome is an uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long standing. The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones. This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated. Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'. This process can be uncomfortable and also result in systemic hypocalcaemia.

### Question 3 of 174

A 75-year-old man presents to referred to the diabetic clinic by his general practitioner with newly identified hyperglycaemia. He had presented with a two month history of polyuria, polydipsia and diarrhoea and was found to have a blood sugar of 18.4 mmol/L. Over this time period he had lost 6kg and now weighed 61kg. His past medical history includes hypertension and a deep vein thrombosis which was diagnosed three months ago. He takes amlodipine 10mg and warfarin.

What is the diagnosis?

[Glucagonoma53%](#)[Type one diabetes mellitus7%](#)[Cushing's syndrome8%](#)[Drug induced diabetes9%](#)[Type two diabetes mellitus23%](#)

Glucagonoma is an uncommon tumour of the pancreatic alpha cells. It can present with new or worsening diabetes mellitus, venous thromboembolism, the classic rash of necrolytic migratory erythema (a painful, pruritic maculopapular rash occurring typically at sites of friction with clothing...) and other symptoms of hyperglucagonaemia (diarrhoea, weight loss, anaemia). Type one diabetes mellitus can of course present with the osmotic symptoms of hyperglycaemia and weight loss but would be unlikely in a patient of this age with no history of auto-immune disease. Type two diabetes mellitus would be uncommon in a non-obese older patient and is less likely to present with osmotic symptoms.

## Glucagonoma

Glucagonomas are small tumours, almost always found in the pancreas, and frequently malignant. The tumours arise from the alpha cells of the pancreas.

They present with diabetes mellitus, venous thrombo-embolism and the classical rash of necrolytic migratory erythema - a red, blistering rash.

A serum level of glucagon  $>1000\text{pg/ml}$  usually suggests the diagnosis, imaging with CT scanning is also required.

Treatment options include surgical resection and octreotide.

### Question 4 of 174

A 56-year-old lady presents with a 3 month history of abdominal pains, low mood and constipation. Past medical history includes hypertension and depression following the death of her husband 2 years ago. Routine blood tests are performed by the GP and upon review the patient is referred into hospital.

Blood tests are as below:

Hb	100 g/l	Na <sup>+</sup>	135 mmol/l
Platelets	$230 \times 10^9/l$	K <sup>+</sup>	4.7 mmol/l
WBC	$10 \times 10^9/l$	Urea	6 mmol/l
Calcium (adjusted)	2.96 mmol/l	Creatinine	110 $\mu\text{mol/l}$
Phosphate	1.35 mmol/l	CRP	30 mg/l
Albumin	35 g/L		

Which diagnostic test should be performed first?

[Parathyroid hormone level 66%](#) [Myeloma screen 14%](#) [CT chest, abdomen and pelvis 7%](#) [Urinary calcium levels 8%](#) [Skeletal X-ray 5%](#)

The two main causes of hypercalcaemia are primary hyperparathyroidism and malignancy.

Parathyroid hormone level will help to differentiate between these two main differentials and help guide further investigations.

### **Hypercalcaemia: causes**

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to number of processes, including; bone metastases, myeloma, PTHrP from squamous cell lung cancer

Other causes include

- sarcoidosis\*
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs: thiazides, calcium containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone\*\*

\*other causes of granulomas may lead to hypercalcaemia e.g. Tuberculosis and histoplasmosis

\*\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

### **Question 5 of 174**

A 51-year-old woman is reviewed in clinic. Two months ago she underwent an operation to remove a medullary thyroid cancer after presenting with diarrhoea and a neck lump. Genetic testing showed she has a mutation of the RET oncogene. The patient reports being well and there are no signs of local recurrence on examination.

What is the most appropriate test to monitor for recurrence?

[Thyroglobulin32%Thyroid transcription factor-17%Chromogranin6%Calcitonin48%S100 protein6%](#)

Medullary thyroid cancer - calcitonin is used for screening, prognosis and monitoring  
S100 protein is used in patients with melanoma. Thyroglobulin is used in other types of thyroid malignancy but not medullary thyroid cancer.

## Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

### Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

### Further information

Type	Notes
Papillary carcinoma	<ul style="list-style-type: none"><li>• Usually contain a mixture of papillary and colloidal filled follicles</li><li>• Histologically tumour has papillary projections and pale empty nuclei</li><li>• Seldom encapsulated</li><li>• Lymph node metastasis predominate</li><li>• Haematogenous metastasis rare</li></ul>

Type	Notes
Follicular adenoma	<ul style="list-style-type: none"> <li>• Usually present as a solitary thyroid nodule</li> <li>• Malignancy can only be excluded on formal histological assessment</li> </ul>
Follicular carcinoma	<ul style="list-style-type: none"> <li>• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.</li> <li>• Vascular invasion predominates</li> <li>• Multifocal disease rare</li> </ul>
Medullary carcinoma	<ul style="list-style-type: none"> <li>• C cells derived from neural crest and not thyroid tissue</li> <li>• Serum calcitonin levels often raised</li> <li>• Familial genetic disease accounts for up to 20% cases</li> <li>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.</li> </ul>
Anaplastic carcinoma	<ul style="list-style-type: none"> <li>• Most common in elderly females</li> <li>• Local invasion is a common feature</li> <li>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.</li> </ul>

#### Question 1 of 168

A 24-year-old lady presents to hospital with increasing confusion. Her parents describe a gradual history of weight loss, lethargy with abdominal cramping. She has no past medical history and is prescribed no regular medications. She lives with her parents. Her mother suffers from hypothyroidism and her father from hypertension which is controlled with bendroflumethiazide.

On examination she is thin, with cool skin and sunken eyes. Her capillary refill time is 3 seconds with dry mucous membranes. Auscultation of her chest reveals bilateral symmetrical vesicular breath sounds. Her abdomen is soft with normal bowel sounds. She is confused with a Glasgow Coma Scale of 14. She has no focal neurology.

Her investigations reveal;

Hb 10.4 g/dL  
 MCV 90 fL  
 WCC  $6.4 \times 10^9/l$   
 Platelets  $170 \times 10^9/l$

105 mmol/L



Na+  
K+ 5.8 mmol/L  
Ur 8.8 mmol/L  
Cr 90 µmol/L  
Glucose 3.9 mmol/L

Urinary Osmolality 108 mmol/L  
Urinary Sodium 67 mmol/L

Chest X ray Clear  
CT Head No intracranial abnormalities

What is the most likely diagnosis?

[Adrenal insufficiency50%Laxative abuse8%Hypothyroidism4%Diuretic use31%SiADH7%](#)

This lady has hypovolaemic hyponatraemia. Sodium can be lost through the gastrointestinal tract, skin or urinary tract. This patient is likely to have renal loss secondary to adrenal insufficiency.

The urinary sodium would be reduced if there were gastrointestinal or skin losses. Also, the patient would be hypokalaemic if there were laxative abuse. The patient would be expected to have hypokalaemia if there were abuse of bendroflumethiazide.

The patient is hypovolaemic and therefore SIADH is excluded, also, hypothyroidism and adrenal insufficiency have not been excluded which would be necessary to make the diagnosis of SIADH.

Hypothyroidism classically presents with weight gain and euvolaemic hyponatraemia.

This patient has adrenal insufficiency. It is possibly of an autoimmune nature with a probable autoimmune hypothyroidism in the immediate family. She has a gradual onset of non-specific symptoms lethargy, weight loss and abdominal symptoms. The hyponatraemia has caused confusion. The blood tests reveal hypoglycaemia, hyponatraemia with hyperkalaemia and normocytic anaemia. Examination revealed signs of hypovolaemia, it also could show skin or mucus membrane pigmentation.

**Addisonian crisis**

## Causes

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococemia)
- steroid withdrawal

## Management

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

## Question 3 of 168

A 24-year-old female presents with one week of progressive and persistent double vision. She reports increasing tiredness at all times of day over the past 2 months and occasional chest tightness associated with palpitations. She has no past medical history. She was also adopted and unaware of any family history. On examination, you find a loss of left eye abduction, right eye upwards gaze, right eye adduction. Systemic examination also reveals bilateral clammy hands and a heart rate of 120 per minute, irregular. Which test is most likely to be diagnostic?

[Autoimmune screen 10% Thyroid function tests 58% CT thorax 10% Anti-acetylcholine receptor antibodies 17% 12 lead ECG 5%](#)

This patient presents with systemic symptoms and a complex ophthalmoplegia, the diagnosis of thyroid eye disease, secondary to Graves disease, is most likely. The important test would be thyroid function tests and also MRI of her orbits, which would almost certainly demonstrate retro-orbital and extraocular muscle inflammation. The severity of the patient's eye disease needs to be assessed: the most frequently used criteria was developed by the American thyroid association, which spells out helpfully NO SPECS

Class 0 No symptoms or signs

Class I Only signs, no symptoms (lid retraction, stare, lid lag)

Class II Soft tissue involvement

Class III Proptosis

Class IV Extraocular muscle involvement

Class V Corneal involvement

## Class VI Sight loss (optic nerve involvement)

Any patient presenting with eye movement weaknesses that cannot be explained by isolated or multiple cranial nerve palsies is called complex ophthalmoplegia. The differentials include myasthenia gravis, mononeuritis multiplex, thyroid eye disease, Kearns-Sayre syndrome, complex progressive external ophthalmoplegia, Miller-Fisher syndrome and botulinum poisoning.

## Thyroid eye disease

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

### Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

### Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

### Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

### Management

- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

### **Monitoring patients with established thyroid eye disease**

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

#### **Question 4 of 168**

A 57-year-old female presents after noticing a lump in her neck. She reports it being non-tender and she is only concerned about it for cosmetic purposes. She reports no other symptoms. Her past medical history includes hypertension and constipation. Her current medications include ramipril, irbesartan, amlodipine and furosemide. No family history is unavailable. On examination, her neck lump is hard, non-tender and measures 2cm by 1 cm, moves with swallowing but not with tongue protrusion. Her heart rate is 84 beats/min and blood pressure 213/130 mmHg. Examination of her joints was unremarkable with no excessive laxity.

Her blood tests are as follows:

Hb	112 g/l
Platelets	349 * 10 <sup>9</sup> /l
WBC	7.2 * 10 <sup>9</sup> /l
Na <sup>+</sup>	138mmol/l
K <sup>+</sup>	4.2 mmol/l
Urea	6.9 mmol/l
Creatinine	72 µmol/l
Adjusted calcium	3.1 mmol/l
Phosphate	0.40 mmol/l

She undergoes an outpatient ultrasound and fine needle aspiration of her neck lump. After her procedure, the recovery nurses were concerned regarding her persistent hypertension and the patient is admitted for further investigation. She develops a mild headache with no visual disturbances, resolving on its own after her blood pressure falls to 182/101 mmHg two hours later. Urinary metanephrine collection was positive.

Which investigation is likely to produce the underlying diagnosis?

[Genetic testing for RET mutation62%](#)[Genetic testing for germline VHL mutation6%](#)[Genetic testing for NF2 mutation on chromosome 229%](#)[CT chest/abdomen/pelvis with contrast16%](#)[Urinary calcium collection6%](#)

The clinical collection of pheochromocytoma and hyperparathyroidism should raise suspicion of multiple endocrine neoplasia type 2a, which is a genetic syndrome of near 100% penetrance caused by a mutation of the RET oncogene. The addition of a thyroid lump makes this scenario more suggestive of MEN 2, with medullary thyroid carcinoma completing the diagnosis. MEN2b is subtly differentiated from MEN2a by the lack of hyperparathyroidism and Marfanoid features. Unlikely MEN 1, genetic screening of family members for hyperparathyroidism and germline mutation is useful for long-term surveillance and monitoring. VHL and NF 2 mutations refer to von-Hippel Lindau syndrome and neurofibromatosis type 2 respectively: VHL presents classically as a combination of retinal haemangioblastomas, renal cell carcinomas and pheochromocytomas while NF2 typically present with intracranial tumours, bilateral Schwannomas almost in all patients.

## Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

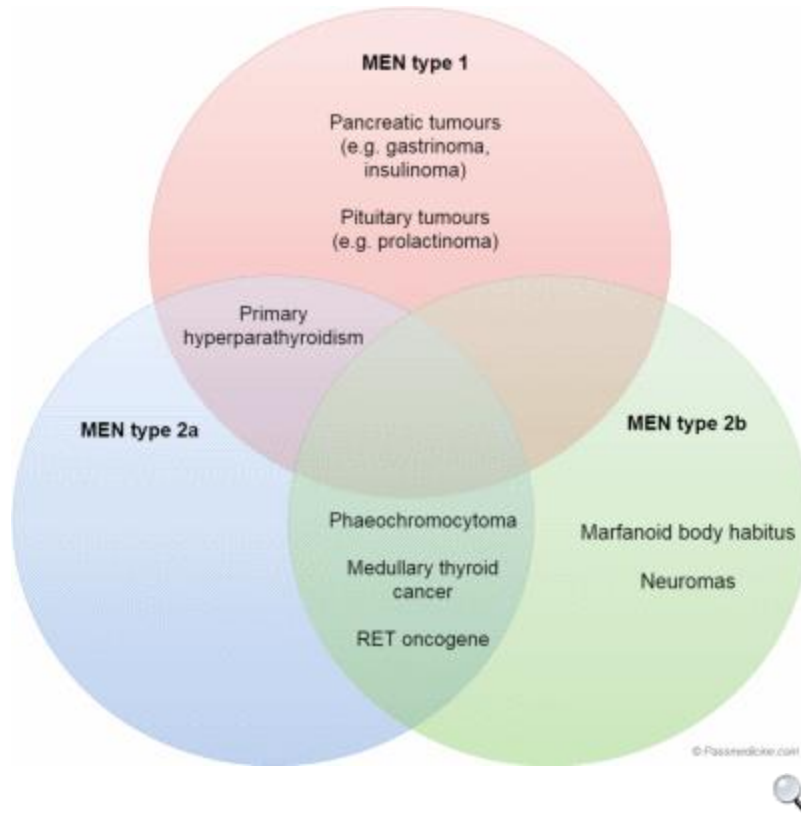
MEN type I	MEN type IIa	MEN type IIb
3 P's		Medullary thyroid cancer
Parathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia	Medullary thyroid cancer (70%)	
Pituitary (70%)	2 P's	1 P
Pancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration)	Parathyroid (60%)	Pheochromocytoma
	Pheochromocytoma	Marfanoid body habitus
Also: adrenal and thyroid		Neuromas
MEN1 gene	RET oncogene	RET oncogene

## MEN type I

## MEN type IIa

## MEN type IIb

Most common presentation = hypercalcaemia



Venn diagram showing the different types of MEN and their associated features

### Question 1 of 164

A 19-year-old woman presents to her GP with a 7 month history of weight loss, diarrhoea and palpitations. The diarrhoea is normal colour and over the last three months she has had roughly 2-3 bowel motions per day. The heart palpitations occur randomly throughout the day and night. She has also noticed that she has recently been getting episodes of feeling very hot and sweaty. She has no other past medical history and her only family history is a mother who has Hashimotos thyroiditis.

On examination, the patient is sweaty and her blood pressure is 130/80 mmHg, pulse is 102 bpm and regular, respiratory rate is 16/min and her oxygen SATs are 98% on air.

Blood tests are performed and reveal:

Hb	135 g/l
Platelets	$220 \times 10^9/l$
WBC	$7.1 \times 10^9/l$
Na <sup>+</sup>	139 mmol/l
K <sup>+</sup>	3.9 mmol/l
Urea	5.1 mmol/l
Creatinine	60 $\mu$ mol/l
Free thyroxine (T4)	28 pmol/l
Thyroid stimulating hormone (TSH)	0.08 mu/l

A thyroid radioisotope scan is performed and reveals a globally reduced uptake.

What is the most likely diagnosis?

[Graves disease24%](#) [Thyrotoxicosis factitia34%](#) [Hashimotos disease15%](#) [De Quervains thyroiditis20%](#) [Atrophic thyroiditis6%](#)

The most likely diagnosis in this case is thyrotoxicosis factitia. This is evidenced by the reduced thyroid uptake on radioisotope scanning, along with the fact she may have easy access to thyroxine her mother would be taking it for her Hashimotos thyroiditis. De Quervains thyroiditis can present with symptoms similar to factitious thyroiditis and a decreased uptake on radioisotope scan, however, the fact the symptom have lasted for 7 months makes this diagnosis unlikely.

## Thyrotoxicosis

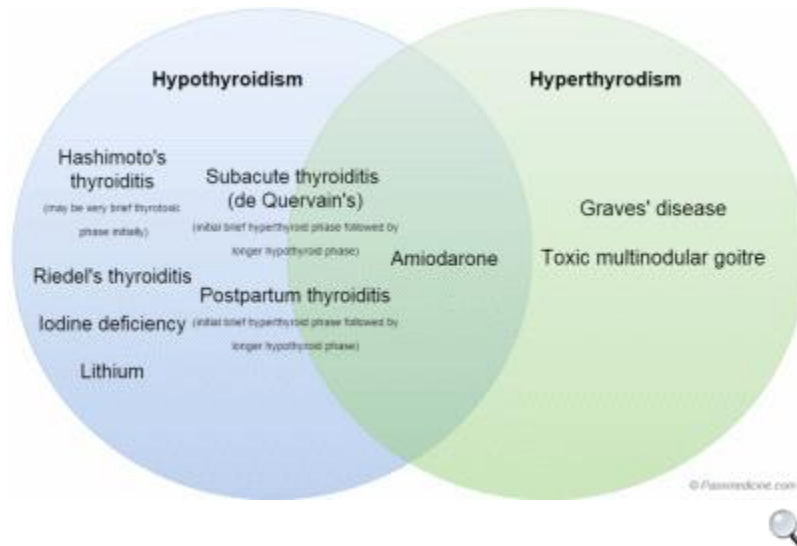
Graves' disease accounts for around 50-60% of cases of thyrotoxicosis.

### Causes

- Graves' disease
- toxic nodular goitre
- acute phase of subacute (de Quervain's) thyroiditis
- acute phase of post-partum thyroiditis
- acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- amiodarone therapy

### Investigation

- TSH down, T4 and T3 up
- thyroid autoantibodies
- other investigations are not routinely done but includes isotope scanning



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

#### Question 2 of 164

A 48-year-old man who was diagnosed with type 2 diabetes mellitus presents for review. During his annual review he was noted to have the following results:

Total cholesterol 5.3 mmol/l  
 HDL cholesterol 1.0 mmol/l  
 LDL cholesterol 3.1 mmol/l  
 Triglyceride 1.7 mmol/l  
 HbA1c 6.4%

A QRISK2 score is calculated showing that he has a 12% 10-year risk of developing cardiovascular disease. His current medication is metformin 500mg tds. According to recent NICE guidelines, what is the most appropriate action?

[Simvastatin 40mg on 7%](#) [Lifestyle advice, repeat lipid profile in 3 months 11%](#) [Atorvastatin 40mg on 17%](#) [Atorvastatin 20mg on 62%](#) [Increase his metformin slowly to 1g tds 4%](#)

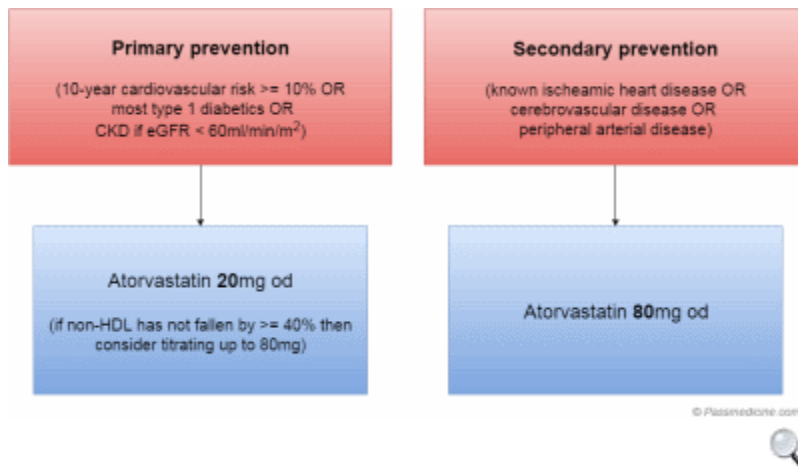


NICE recommend the following when considering the use of statins in patients with type 2 diabetes mellitus:

*Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD.*

## Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.



Graphic showing choice of statin.

### Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged ≤ 84 years. Patients ≥ 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria

- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

## Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checking to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples does not need to be fasting.

In the vast majority of patient the cholesterol measurements will be fed into the QRISK2 tool. If however the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if the total cholesterol concentration is  $> 7.5$  mmol/l and there is a family history of premature coronary heart disease. They also recommend referring people with a total cholesterol  $> 9.0$  mmol/l or a non-HDL cholesterol (i.e. LDL) of  $> 7.5$  mmol/l even in the absence of a first-degree family history of premature coronary heart disease.

## Interpreting the QRISK2 result

Probably the headline changes in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

**NICE now recommend we offer a statin to people with a QRISK2 10-year risk of  $\geq 10\%$**

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

## Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
- → older than 40 years, or
- → have had diabetes for more than 10 years or
- → have established nephropathy or
- → have other CVD risk factors

### Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

### Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

### Follow-up of people started on statins

NICE recommend we follow-up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

### Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

#### Cardioprotective diet

- total fat intake should be  $\leq 30\%$  of total energy intake
- saturated fats should be  $\leq 7\%$  of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible

- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

#### Physical activity

- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do musclestrengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

#### Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

#### Alcohol intake

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

#### Smoking cessation

- smokers should be encouraged to quit

#### Question 5 of 164

A 50-year-old woman with a history of Grave's disease is reviewed on the surgical ward some 12hrs after parathyroidectomy. She has begun suffering from episodes of carpopedal spasm and pins and needles affecting both hands and around her mouth. On examination on the ward, her blood pressure is 115/72 mmHg, and pulse is 88 beats per minute. Her serum calcium is

measured at 1.85 mmol/l.

Which of the following is the most appropriate intervention?

[Intravenous diazepam4% Intravenous calcium75% Intravenous magnesium9% Oral calcium7% Oral vitamin D4%](#)

This patient has symptomatic hypocalcaemia, most likely due to an acute fall in parathyroid hormone after surgery. This is considered a medical emergency and calcium replacement IV is essential:

IV calcium gluconate is administered initially with 20 ml of 10% calcium gluconate in 50-100 ml of 5% dextrose IV, given over 10 minutes with ECG monitoring. This can be repeated until the patient is asymptomatic. It should be followed up with a calcium gluconate infusion where 100ml of 10% calcium gluconate is diluted in 1 litre of normal saline or 5% dextrose and infused at 50-100 ml/hr.

Not intervening with respect to the electrolyte disturbance risks significant sequelae including cardiac arrhythmia, diazepam is therefore not appropriate. IV magnesium is most useful where hypocalcaemia is resistant to correction, and oral interventions would take too long to elevate serum calcium levels.

## **Hypocalcaemia: causes and management**

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

### **Causes**

- vitamin D deficiency (osteomalacia)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion

Acute pancreatitis may also cause hypocalcaemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

### **Management**

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

#### Question 6 of 164

A 54-year-old man with a history of type 2 diabetes is recovering on the surgical ward having suffered an episode of acute pancreatitis some 4 days earlier. Medication for glucose control includes metformin, dapagliflozin and liraglutide. On examination his blood pressure is 135/80 mmHg, pulse is 72 and regular. His body mass index is 35 kg/m<sup>2</sup>. A recent HbA1c is 63 mmol/mol, renal function is reported as normal. Which of the following is the correct course of action with respect to his long term blood glucose lowering medication?

[Stop metformin8%](#)[Stop dapagliflozin27%](#)[Stop liraglutide41%](#)[Continue usual medication18%](#)[Stop metformin and liraglutide6%](#)

This patient is now stable following his episode of pancreatitis, but in view of a number of studies suggesting an association between GLP-1 agonist prescription and pancreatitis, it should be withdrawn in patients who suffer pancreatitis whilst on therapy, and not instituted in patients who have a history of the disease. For this reason liraglutide should be withdrawn.

With respect to metformin, it should potentially be discontinued during periods of increased risk of tissue hypoxia, (e.g. during the acute period of pancreatitis), but there is no indication it should be omitted over the longer term. In regards to metformin and renal impairment, guidance has recently been revised to support metformin initiation at glomerular filtration rate as low as 45ml/min.

#### Question 7 of 164

A 28-year-old woman presents with flu-like symptoms, palpitations and pain over the anterior neck over the past 2-3 weeks. She has also suffered rapid weight loss and feels increasingly anxious that there may be something seriously wrong with her. Her thyroid-stimulating hormone has been measured at <0.05 IU by her GP. On examination her blood pressure is 128/82 mmHg, her pulse is 95 beats per minute and regular, and she has a fine tremor. There is mild tenderness over the anterior neck. Body mass index is 22 kg/m<sup>2</sup>

Which of the following would you also expect to find?

[Erythema nodosum4%](#) [Exophthalmos7%](#) [Multiple small thyroid nodules on ultrasound scan6%](#) [Positive anti-thyroid antibodies17%](#) [Reduced uptake on thyroid scintigraphy66%](#)

The most likely diagnosis, given the history of 2-3 weeks of flu-like symptoms and suppressed TSH, is subacute thyroiditis where thyroid inflammation drives increased release of stored thyroid hormone, rather than the clinical picture being due to overproduction of T3 and T4. Symptoms of hyperthyroidism should be managed with beta blockade as required, and there is no role for thioamides. Pain over the thyroid can be managed with non-steroidal anti-inflammatory drugs. After a period of hyperthyroidism, rebound hypothyroidism may be seen, followed by a recovery to euthyroidism.

Erythema nodosum is not associated with subacute thyroiditis. Exophthalmos and positive anti-thyroid antibodies are associated with autoimmune thyroid disease. Multiple small thyroid nodules are a feature of multinodular goitre.

Question 8 of 164

An 82-year-old woman presents to the emergency department with chronic neck pain after having been referred by her GP. She has been seeing her GP for pain which has been progressively worsening and noticed that her hands have both started to become weak. This has caused her to struggle with daily activities so she became concerned. She has a past medical history of hysterectomy, hypertension and hypothyroidism. She has never smoked and drinks roughly one unit of alcohol per week. On examination, she has reduced power in both her hands and tenderness over the cervical spine. She has no IV access currently. An urgent MRI of the whole is arranged which shows an infiltrative lesion at C2 and spinal cord compression. She is being referred urgently for a neurosurgical and oncological opinion. What treatment should be prescribed?

[Oral prednisolone3%](#) [IV hydrocortisone4%](#) [Oral dexamethasone35%](#) [IV dexamethasone50%](#) [IV methylprednisolone7%](#)

The correct answer is oral dexamethasone. This patient has unfortunately developed evidence of metastatic cord compression as a presentation of undiagnosed malignancy. This is an oncological emergency and needs urgent referral to both oncology, who may arrange radiotherapy, and neurosurgery, who may arrange for surgical decompression. In the interim, the patient should be treated with corticosteroids. Dexamethasone is advised as it has the highest glucocorticoid activity and is preferred when the aim is to reduce neurological compression. Oral dexamethasone is preferred to IV as the efficacy is the same, but prescribing it IV may cause

delays due to greater difficulties in administration. If the patient is unable to take it orally then IV should be used.

## Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

<b>Minimal glucocorticoid activity, very high mineralocorticoid activity,</b>	<b>Glucocorticoid activity, high mineralocorticoid activity,</b>	<b>Predominant glucocorticoid activity, low mineralocorticoid activity</b>	<b>Very high glucocorticoid activity, minimal mineralocorticoid activity</b>
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

## Side-effects

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

### Glucocorticoid side-effects

- endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, hyperlipidaemia
- Cushing's syndrome: moon face, buffalo hump, striae
- musculoskeletal: osteoporosis, proximal myopathy, avascular necrosis of the femoral head
- immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis
- psychiatric: insomnia, mania, depression, psychosis
- gastrointestinal: peptic ulceration, acute pancreatitis
- ophthalmic: glaucoma, cataracts
- suppression of growth in children
- intracranial hypertension



## Mineralocorticoid side-effects

- fluid retention
- hypertension

## Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have:  
received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses

## Subacute (De Quervain's) thyroiditis

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;

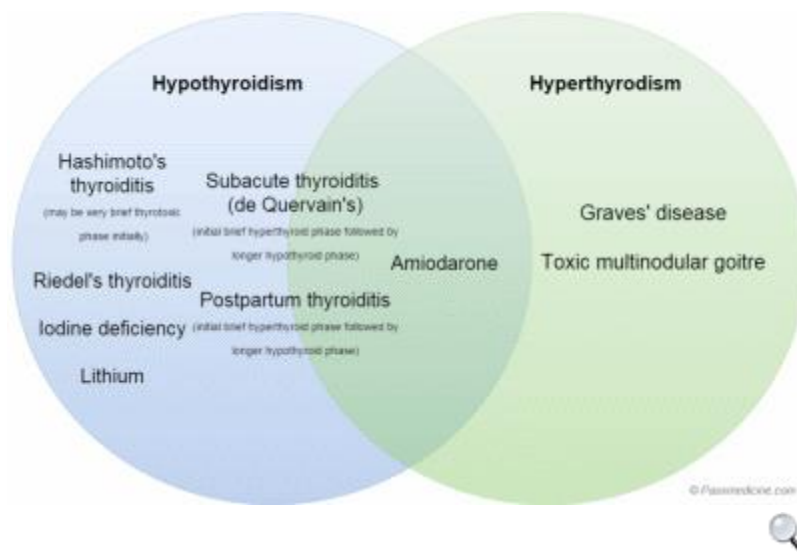
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

## Investigations

- globally reduced uptake on iodine-131 scan

## Management

- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

#### Question 9 of 164

A 45-year-old woman with chronic alcohol abuse admitted 3 days ago for nausea and severe diarrhoea now complains of peri-oral and finger tingling. She was admitted for hydration after 1 week of severe watery diarrhoea. She has been receiving intravenous hydration and dextrose but has not been able to take oral nutrition secondary to continued nausea. Her blood pressure is 130/74 mmHg, pulse is 68/min, and respiratory rate is 16/min. She is afebrile.

Physical examination is significant for facial twitching on percussion of her facial nerve just anterior to the ear, as well as the induction of carpal spasm after the inflation of a blood pressure cuff on her arm.

Which of the following is most likely to have caused these findings?

[Hyperuricaemia5%](#) [Hypernatraemia4%](#) [Hypomagnesaemia66%](#) [Hypophosphataemia21%](#) [Hypouricaemia4%](#)

This patient is displaying classic signs of hypocalcaemia, including hyperexcitability of her facial nerve (Chvostek's sign), induced carpal spasm (Trousseau's sign), and tingling of the extremities and lips. Calcium homeostasis is a complicated process involving PTH, vitamin D, albumin and numerous electrolytes. Acquired hypoparathyroidism is the most common form of true hypocalcaemia, most often occurring transiently after thyroid surgery or after the removal of a parathyroid adenoma. Occasionally, hypomagnesaemia can produce hypocalcaemia by decreasing both the body's production of PTH and its sensitivity to the hormone. In this case, it is likely that the patient became magnesium depleted from her course of watery diarrhoea, likely baseline poor nutritional status and alcohol abuse.

Choice 1: Hyperuricaemia is not a cause of hypocalcaemia. Chronic kidney disease, however can lead to hypocalcaemia in the setting of secondary hyperparathyroidism, but there is no evidence of renal failure in this patient.

Choice 2: Fluid balance (hyper- or hyponatraemia) does not play a role in calcium homeostasis.

Choice 4: Hypophosphataemia is not a cause of hypocalcaemia. Actually, hypocalcaemia often leads to hyperphosphataemia secondary to increased PTH-mediated bone resorption. Elevations in phosphate may also contribute to hypocalcaemia by complexing with circulating calcium and suppressing conversion of 25-OH to 1, 25-OH vitamin D.

Choice 5: Urate levels do not affect calcium homeostasis.

## **Hypocalcaemia: causes and management**

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

### **Causes**

- vitamin D deficiency (osteomalacia)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion

Acute pancreatitis may also cause hypocalcaemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

### **Management**

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

### Question 1 of 155

A 31-year-old ICU nurse is brought to the Emergency Department following an unresponsive episode during a busy shift at work. His colleague described him becoming pale and sweating profusely, before collapsing to the ground and becoming unresponsive. No jerking movements were observed.

His past medical history is unremarkable and he takes no regular medications.

On examination, the patient is pale and sweaty. His GCS is 9/15. His pulse is 106bpm and his blood pressure is 118/67mmHg. His chest is clear and his abdomen is soft and non-tender. There are linear, well-healed scars over the volar aspects of both forearms. His capillary blood glucose measurement is 1.6 mmol/l.

The patient is given 250ml of 10% dextrose solution through a large-bore peripheral venous cannula and his GCS improves to 15/15. His initial blood test results are:

Hb	135 g/l	Na <sup>+</sup>	139 mmol/l
Platelets	221 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.5 mmol/l
WBC	7.1 * 10 <sup>9</sup> /l	Urea	4.8 mmol/l
Neuts	5.3 * 10 <sup>9</sup> /l	Creatinine	81 µmol/l
Lymphs	1.2 * 10 <sup>9</sup> /l	CRP	13 mg/l
Eosin	0.03 * 10 <sup>9</sup> /l		

Glucose 1.2 mmol/l

Insulin 254 pmol/l (<174 pmol/l)

C-peptide 1.8 mmol/l (0.26 - 1.03 mmol/l)

What is the most likely cause of the hypoglycaemia?

[Exenatide poisoning4%](#) [Insulin poisoning25%](#) [Insulinoma27%](#) [Sulfonylurea poisoning42%](#) [Hepatic glycogen depletion due to missed meal breaks4%](#)

Profound hypoglycaemia in the context of elevated C-peptide and insulin levels indicates excessive secretion of pancreatic insulin. These abnormalities could be secondary to either sulfonylurea poisoning or insulinoma. Insulinoma is extremely rare, however, and it is likely that sulfonylureas would be readily available to the patient described. Option 4 is, therefore, the correct answer in this case.

Surreptitious administration of exogenous insulin would lead to low C-peptide levels as endogenous insulin secretion is suppressed by the resultant hypoglycaemia.

Exenatide is GLP-1 mimetic that augments pancreatic insulin release by replicating the incretin effect. It does not affect the counterregulatory response to hypoglycaemia, however, and

glucagon levels quickly return to normal if low blood glucose levels decrease. As a result, exenatide overdose does not tend to cause significant hypoglycaemia, although GI symptoms can be prominent.

It is most unlikely that hepatic glycogen depletion secondary to prolonged fasting in a healthy individual would lead to blood glucose levels this low.

## **Hypoglycaemia**

### **Causes**

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol

### **Other possible causes in children**

- nesidioblastosis - beta cell hyperplasia

### **Question 1 of 154**

A 24 year old female patient attends the young persons diabetes clinic for a routine follow up. She developed type 1 diabetes mellitus 4 years ago, presenting in DKA at that time. Since then she has been well controlled on carbohydrate counting and basal bolus insulin. Since starting treatment with insulin she has developed vitiligo on her hands and feet which causes her some distress. She is very aware of her skin pigmentation due to her vitiligo and reports on this encounter that she feels her skin in her armpits has gotten darker. She also reports vague symptoms of nausea, weight loss and muscle weakness. She has had to stop playing badminton with her friends due to occasional light-headedness and having fainted once. Her blood sugar diary shows an early morning (fasting) level of 7.1. The highest sugar level recorded is 13.2 with the occasional dip below 4.0.

Examination reveals hyperpigmentation of the axilla bilaterally. There is vitiligo present in both hands and feet but this is consistent with previous examinations. Abdominal examination reveals generalised tenderness with no guarding, some abdominal striae are seen.

Some simple investigations are carried out

Blood Pressure

Lying - 110/76mmHg

Standing 1 minute 94/70mmHg

Standing 3 minutes 86/66mmHg

Hb 12.0 g/dl

Platelets  $321 \times 10^9/l$

WBC  $5.3 \times 10^9/l$

Na<sup>+</sup> 128 mmol/l

K<sup>+</sup> 5.6 mmol/l

Urea 5.6 mmol/l

Creatinine 82  $\mu$ mol/l

Bicarbonate 16mmol/l

Random glucose 4.1 mmol/l

HbA1c 58mmol/mol (7.5%)

Given the most likely diagnosis, what is the most important immediate management?

IV Hypertonic (3%) saline 4% IV 0.45% Saline + 5% Dextrose 5% Oral Glucose drink 5% IV Bicarbonate (1.24%) Infusion 4% 100mg IV hydrocortisone 82%

The symptoms and findings above are highly suggestive of Addison's Disease with the early signs of Addisonian Crises. The immediate management is to give steroids to replace the deficiency that is present. The patient above will also need adequate rehydration therapy. Once steroids are given they may be able to take this orally, but in reality most patients would be started on intravenous 0.9% saline. The results shown above do not suggest the presence of hypoglycaemia and after the injection of steroids this blood sugar level is likely to increase.

In this instance the Addison's Disease is part of the autoimmune polyendocrine syndrome type 2 (also known as Schmidt's Syndrome). In a patient presenting with more than one endocrine or autoimmune disorder there should be some consideration of other possible disorders. Some would advocate the testing for antibodies to 21-hydroxylase (a feature of Addison's disease) to try and pre-empt the development of that condition and to allow for treatment before a dangerous crisis occurs.

**Addisonian crisis**

## Causes

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococemia)
- steroid withdrawal

## Management

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

## Question 2 of 154

A 56-year-old Kenyan female has a 6 month history of weight loss of 5 kg associated with episodic severe colicky abdominal pain not associated with eating or bowel opening.

Na <sup>+</sup>	126 mmol/l
K <sup>+</sup>	6.5 mmol/l
Urea	14.3 mmol/l
Creatinine	157 µmol/l
Glucose	3.2 mmol/l
T4	7.5 pmol/L (NR 9-20 pmol/L)
TSH	11.2 mIU/L (NR 0.3-6.0 mIU/L)

Thyroid antibodies are not detected.

What is the most likely diagnosis?

[Hypopituitarism12%](#)[MEN type 118%](#)[Autoimmune adrenal failure26%](#)[Primary hypothyroidism4%](#)[Adrenal failure secondary to TB39%](#)

This patient has adrenal failure (hyponatraemia, hyperkalaemia, raised urea and creatinine, hypoglycaemia). Addison's disease in the western world is mostly due to autoimmune causes (associated with adrenal auto-antibodies and anti-thyroid antibodies) however in the developing world TB is the most common cause.

Diagnosis is confirmed with the synacthen test (deliver tetracosactrin followed by measuring serum cortisol at 0, 30, 60 minutes later - a normal result is an increase in cortisol to  $>250\text{nmol/L}$  at 30mins and  $>550\text{nmol/L}$  by 60mins). ACTH levels are also raised in primary adrenal failure and abdominal X ray may show adrenal calcification from TB.

Treatment is with hydrocortisone 20-30mg a day with fludrocortisone 0.1mg if hypotensive.

The low T4 may indicate hypothyroidism but the raised TSH excludes hypopituitarism. A low T4 is seen in Addison's disease in the absence of functional hypothyroidism, and corrects with steroid replacement.

## **Addison's disease**

Autoimmune destruction of the adrenal glands is the commonest cause of primary hypoadrenalism in the UK, accounting for 80% of cases

### Features

- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases), vitiligo, loss of pubic hair in women, hypotension
- crisis: collapse, shock, pyrexia

## **Other causes of hypoadrenalism**

### Primary causes

- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

### Secondary causes

- pituitary disorders (e.g. tumours, irradiation, infiltration)

### Exogenous glucocorticoid therapy



### Question 3 of 154

A 30-year-old female, who was diagnosed two months earlier with Graves disease and was started on carbimazole 40 mg per day , presented complaining of sore throat.

Investigations reveal:

Haemoglobin	11.5 g/dl
MCV	80 fl
White cell count	$4.2 \times 10^9/l$
Neutrophils	$2.0 \times 10^9/l$
Lymphocytes	$2.3 \times 10^9/l$
Basophils	$0.08 \times 10^9/l$
Eosinophils	$0.1 \times 10^9/l$
Platelets	$170 \times 10^9/l$

What is the most appropriate treatment for this patient?

[Discontinue carbimazole and give propylthiouracil23%](#)[Discontinue carbimazole and give radioactive iodine6%](#)[Discontinue carbimazole and give antibiotics14%](#)[Reduce the dose of carbimazole14%](#)[Continue carbimazole 43%](#)

Patients taking carbimazole may develop neutropaenia (although the incidence is very low) so they are warned about a sore throat while taking the medication.

This patient developed a sore throat but her total white cell count and differential are normal, so she should be reassured and continue carbimazole.

If there is neutropaenia, carbimazole should be discontinued and substituted by propylthiouracil till the neutrophil count has recovered and then the patient is planned for radioactive iodine.

## Carbimazole

Carbimazole is used in the management of thyrotoxicosis. It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.

Mechanism of action

- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production
- in contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5'-deiodinase which reduces peripheral conversion of T4 to T3

#### Adverse effects

- agranulocytosis
- crosses the placenta, but may be used in low doses during pregnancy

#### Question 4 of 154

A 60 year old woman had a thyroid function test requested by her General Practitioner after reporting some symptoms of mild lethargy. This had unexpectedly demonstrated a suppressed Thyroid Stimulating Hormone level (0.25 microU / L) but normal free T4 level (14.1 pmol / L). During further consultation, the patient denied any heat intolerance, weight loss, diarrhoea, hair or skin changes, palpitations or eye symptoms.

The patient had had a hysterectomy without oophorectomy at age 45 as treatment for menorrhagia secondary to fibroids. She remember reaching menarche at around the age of 13 or 14 years. There was no significant family history of coronary artery disease. The patient reported her mother had suffered a fractured neck of femur at the age of 75 years following a fall. The patient was a retired school teacher with an active lifestyle. She had never smoked and drank very little alcohol.

Examination showed no evidence of a goitre, no fine tremor and no lid lag. External examination of the eyes was unremarkable. Cardiovascular and respiratory examination was unremarkable.

The GP requested some further basic investigations and then repeated blood tests 2 months after the original test. At this time, the patient reported her previous symptoms of lethargy had improved; with hindsight she attributed this to grief due to the recent death of a close friend.

Ambulatory blood pressure monitoring: average blood pressure 125 / 75 mmHg

ECG: sinus rhythm at 75 bpm; normal axis; no abnormality of QRS, ST interval or T waves.

Haemoglobin	12.8 g / dL
White cell count	$6.5 \times 10^9/l$
Platelets	$206 \times 10^9/l$
Urea	6.2 mmol / L
Creatinine	95 micromol / L

Sodium	137 mmol / L
Potassium	4.0 mmol / L
C-reactive protein	< 1
Parathyroid hormone	3.7 pmol / L (reference 1.2-5.8)
Thyroid-stimulating hormone	0.21 microU / L (reference 0.4-5.0)
T4 free serum	13.8 pmol / L (reference 8.5-15.2)
T3 free serum	5.6 pmol / L (reference 3.5-6.5)
HbA1C	5.6 % (reference 4-6)
Total cholesterol	4.0 mmol / L
LDL cholesterol	1.8 mmol / L
HDL cholesterol	1.9 mmol / L

What is the most appropriate management of the deranged thyroid function tests?

[DEXA scan34%](#)[Thyroid ultrasound37%](#)[Start treatment with simvastatin8%](#)[Radioiodine therapy5%](#)[Treat with propylthiouracil16%](#)

The patient has subclinical hyperthyroidism with persistently suppressed TSH levels but normal serum thyroid hormone levels and with no clinical evidence of thyrotoxicosis. This usually occurs in the setting of thyroid overactivity due to Graves' disease or autonomously functioning thyroid nodules sufficient to suppress pituitary TSH secretion but insufficient to cause an elevation of circulating hormones. Progression to overt hyperthyroidism occurs in 1-3 % of elderly patients per year.

The main risk of subclinical hyperthyroidism is its effects on heart and bone health with increased risk of atrial fibrillation and hip fractures. The American Association of Clinical Endocrinologists recommends that treatment is considered in patients with a persistently low TSH level if they are older than 65 years or are at risk of osteoporosis or heart disease.

This patient has a low level of cardiac risk factors with a low risk lipid profile. Assessment of her osteoporosis risk is complicated by her hysterectomy preventing knowledge of her age at menopause. Therefore, a DEXA scan is appropriate next line management to quantify her osteoporosis risk and inform the decision as to whether or not to treat the sub-clinical hyperthyroidism.

Thyroid ultrasound would not influence decision to treat at this stage and so is not required.

Weetman A. Investigating low thyroid stimulating hormone (TSH) level. BMJ 2013;347:f6842.

## Subclinical hyperthyroidism

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. It is defined as:

- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually  $< 0.1 \text{ mu/l}$ )

### Causes

- multinodular goitre, particularly in elderly females
- excessive thyroxine may give a similar biochemical picture

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (atrial fibrillation) and bone metabolism (osteoporosis). It may also impact on quality of life and increase the likelihood of dementia

### Management

- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention
- a reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission

### Question 5 of 154

A 52 year-old woman presents with a two day history of nausea and fever. On admission she is confused and her husband states that she was recovering from a recent upper respiratory tract infection and sore throat. He also mentions she has previously been experiencing episodes of diarrhoea and palpitations over the last three months.

Examination reveals a temperature of  $40.6^{\circ}\text{C}$ , pulse rate of 160 beats per minute and blood pressure of 110/70 mmHg. Her pulse is irregularly irregular. Heart sounds 1 and 2 are present with no added sounds, lung fields are clear and her abdomen is soft and none tender, with bowel sounds being present.

Blood tests are taken and reveal:

Hb	13.2 g/dL
Platelets	$180 \times 10^9/\text{l}$
WBC	$10.2 \times 10^9/\text{l}$

Na <sup>+</sup>	135 mmol/l
K <sup>+</sup>	4.2 mmol/l
Urea	7.2 mmol/l
Creatinine	132 µmol/l
Thyroid stimulating hormone (TSH)	0.03 mu/l
Free thyroxine (T4)	31 pmol/l
Total thyroxine (T4)	220 nmol/l

What is the most appropriate immediate treatment?

[Carbimazole, corticosteroids and propranolol15%](#) [Carbimazole and propranolol20%](#) [Radio-iodine, corticosteroids and propranolol7%](#) [Carbimazole and corticosteroids6%](#) [Propylthiouracil, propranolol and carbimazole11%](#)

This patient is having a thyrotoxic storm (hyperthyroid crisis) a rare medical emergency that is caused by an exacerbation of hyperthyroidism and characterised by decompensation of one or more organ systems in people with untreated or poorly treated hyperthyroidism. The precipitating cause is most commonly infection, as with this case, although it is important to check for other causes. The patient above is in atrial fibrillation and shows signs of renal impairment due to dehydration. First line treatment for this medical emergency is carbimazole, corticosteroids and propranolol, although chlorpromazine can be added for severe anxiety.

## Thyroid storm

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm

Clinical features include:

- fever > 38.5°C
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test

## Management

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

#### Question 1 of 148

You receive a phone call from a general practitioner regarding a 50 year-old man who has had thyroid function tests performed for a history of weight loss. There is no history of illicitly taking levothyroxine. His results show : TSH 0.01 mIU/L, T4 8.5 ug/dL. You should advise which of the following:

[Admit for urgent MRI head18%](#)[Repeat the bloods and include parathyroid hormone \(PTH\)9%](#)[Add on T3 as this may represent T3 toxicosis60%](#)[Start radio-iodine treatment immediately5%](#)[Start thyroxine replacement8%](#)

In approximately 5% of patients with clinical and biochemical hyperthyroidism T3 may be elevated prior to T4. This is known as T3 toxicosis.

When both free hormones are normal but TSH is low, the term subclinical thyrotoxicosis can be applied.

Radio-iodine treatment should never be started without discussion with the patient and is only used prior to carbimazole in certain circumstances. An MRI head would be part of the work up for secondary hyperthyroidism. PTH would not be useful in this circumstance and starting thyroxine would not be a good idea! T3 toxicosis is treated in the same manner as T4 hyperthyroidism.

### **Subclinical hyperthyroidism**

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. It is defined as:

- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually  $< 0.1$  mu/l)

### Causes

- multinodular goitre, particularly in elderly females
- excessive thyroxine may give a similar biochemical picture

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (atrial fibrillation) and bone metabolism (osteoporosis). It may also impact on quality of life and increase the likelihood of dementia

### Management

- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention
- a reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission

### Question 2 of 148

A 53-year-old woman comes for review in the general medical clinic. She was diagnosed with type 2 diabetes mellitus six months ago after having developed fatigue and polyuria. She also has hypothyroidism but no other comorbidities. She was started on metformin 500mg twice daily struggled to cope due to gastrointestinal side effects such as diarrhoea. What is the most appropriate action?

[Reduce to metformin 500mg once daily8%](#)[Change to dipeptidyl peptidase-4 inhibitor9%](#)[Trial of modified release metformin54%](#)[Change to sulfonylurea25%](#)[Change to pioglitazone4%](#)

The correct answer trial of modified release metformin. NICE guidelines advise to offer standard release metformin as the first-line treatment for type 2 diabetes and to gradually increase the dose to minimise the risk of gastrointestinal side effects. If gastrointestinal side effects are not tolerated, then a trial of modified release metformin would be appropriate. If metformin is not tolerated at all then a dipeptidyl peptidase-4 inhibitor, sulfonylurea or pioglitazone would be indicated.

Source:

'Type 2 diabetes in adults: management.' NICE guideline [NG28]. The National Institute for Health and Care Excellence, December 2015.

## **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

### **Dietary advice**

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

### **HbA1c targets**

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on *'a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes'*
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:



Lifestyle or single drug treatment

<b>Management of T2DM</b>	<b>HbA1c target</b>
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

Practical examples

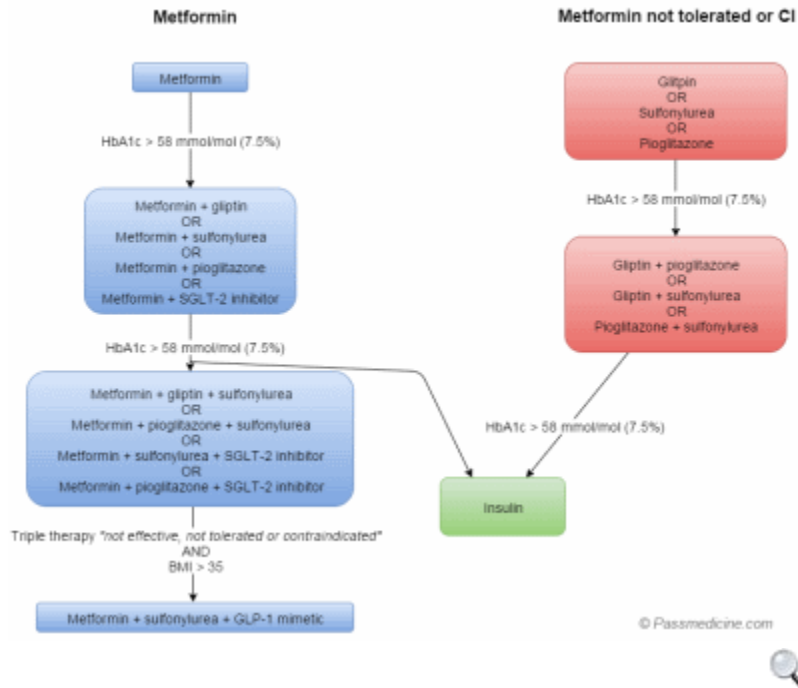
- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

<b>Management of T2DM</b>	<b>HbA1c target</b>
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

## **Drug treatment**

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



### Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
  - → SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  - → metformin + gliptin + sulfonylurea
  - → metformin + pioglitazone + sulfonylurea
  - → metformin + sulfonylurea + SGLT-2 inhibitor
  - → metformin + pioglitazone + SGLT-2 inhibitor
  - → OR insulin therapy should be considered

### Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
  - → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or

- → BMI < 35 kg/m<sup>2</sup> and for whom insulin therapy would have significant occupational implications or

weight loss would benefit other significant obesity-related comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

### Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

### Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

### Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: *'Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

### Risk factor modification

#### Blood pressure

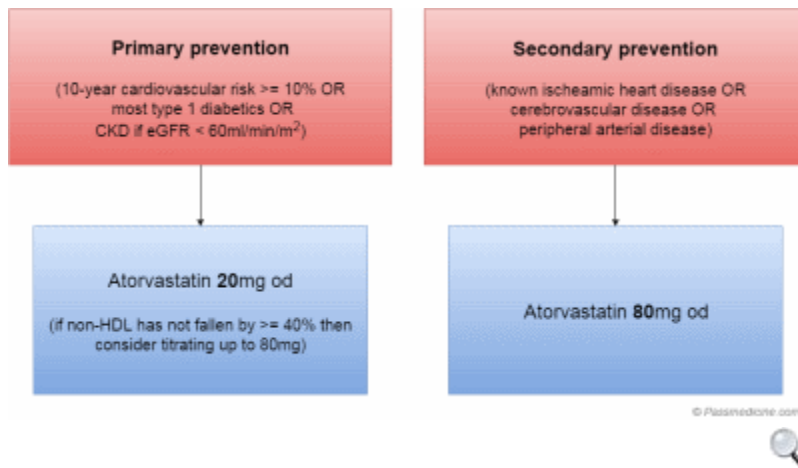
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

### Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



Graphic showing choice of statin.

\*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

### Question 3 of 148

A 37-year-old female presents with 4 days of generally unwell and a recent dysuria. Her urine is foul smelling and dark. She is a known type 1 diabetic with a long-standing subcutaneous insulin regime. Her pH on admission was 7.24, bicarbonate 8 mmol/l and blood glucose 32 mmol/l. Urinary dip leucocytes 2+, nitrites 2+ and 4+ ketones. She was started on treatment for diabetic ketoacidosis with intravenous fluids and fixed rate insulin. She also has intravenous antibiotics for a urinary source of sepsis. You are asked to review her blood sugars at 4 hours after treatment

was initiated. What should be the aim in managing hyperglycaemia in a diabetic ketoacidosis patient?

Reduce blood glucose to under 14 mmol/l as quickly as possible10%Reduce blood glucose by 3mmol/l per hour57%Reduce blood glucose by 6 mmol/l per hour20%Aim blood glucose above 18 mmol/l6%Blood glucose does not require monitoring if insulin infusion is running7%

The most recent guidelines by the Joint British Diabetes Societies Inpatient Care Group in September 2012 recommends a reduction in blood glucose of 3 mmol/l per hour until BM reaches 14 mmol/l, at which point 5% dextrose should be considered as the intravenous fluid of choice. Rapid glucose lowering should be avoided: the rapid flux in osmolality can result in significant cerebral oedema and resultant cerebral damage.

## Diabetic ketoacidosis

Diabetic ketoacidosis may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction

### Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

## Diagnostic criteria

### American Diabetes Association (2009)

#### Key points

- glucose > 13.8 mmol/l
- pH < 7.30
- serum bicarbonate <18 mmol/l
- anion gap > 10

### Joint British Diabetes Societies (2013)

#### Key points

- glucose > 11 mmol/l or known diabetes mellitus
- pH < 7.3
- bicarbonate < 15 mmol/l
- ketones > 3 mmol/l or urine ketones ++ on

**American Diabetes Association  
(2009)**

- ketonaemia

**Joint British Diabetes Societies (2013)**

dipstick

**Management**

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia

**JBDS example of fluid replacement regime for patient with a sSystolic BP on admission 90mmHg and over**

<b>Fluid</b>	<b>Volume</b>
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

**JBDS potassium guidelines**

<b>Potassium level in first 24 hours (mmol/L)</b>	<b>Potassium replacement in mmol/L of infusion solution</b>
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

**Complications of DKA and its treatment**

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema\*, hypokalaemia, hypoglycaemia

- acute respiratory distress syndrome
- acute kidney injury

\* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

#### Question 6 of 148

A 20-year-old female presented to the accident and emergency department with severe abdominal pain, vomiting and lethargy. On further questioning she stated that she had been generally unwell for the last four months during which time she lost 10 Kg in weight and had been tired all the time.

Last month she has been diagnosed with hypothyroidism and was prescribed levothyroxine 50 mcg daily.

Her mother and sister have hypothyroidism and take thyroxine. On examination, she looks unwell and dehydrated.

Her pulse is 105 beats per minute and blood pressure is 70/40 mmHg

Her temperature is 37.6°C and BMI is 19 kg/m<sup>2</sup>. Cardiovascular, respiratory and abdominal examination were normal. Investigations done last month showed:

Hb 9.5 g/dl

MCV 105 fl

Platelets  $190 \times 10^9/l$

WBC  $4.5 \times 10^9/l$

Serum free T4 8.5 pmol/l

Serum TSH 5.5 mU/l

While awaiting new investigations, what is the most appropriate immediate treatment for this patient?

[Intravenous glucose 10%5%](#)[Intravenous normal saline14%](#)[Intravenous normal saline and antibiotics6%](#)[Intravenous normal saline and hydrocortisone69%](#)[Intravenous thyroxine6%](#)

This patient presented with Addisonian crisis (abdominal pain, vomiting, dehydration and hypotension). She has been complaining of tiredness and weight loss (which are features of

Addison's disease) for four months but what precipitated the crisis is the thyroxine given for the presumed hypothyroidism.

Actually, a slightly raised TSH and a decreased T4 are features of primary hypoadrenalism and do not necessarily indicate frank hypothyroidism.

This is a medical emergency and should be treated immediately with intravenous normal saline and hydrocortisone. Thyroxine should not be given as it will exacerbate the condition.

Her low haemoglobin and high MCV may point towards pernicious anaemia which is an autoimmune disease seen sometimes in association with Addison's disease.

## **Addisonian crisis**

### **Causes**

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococemia)
- steroid withdrawal

### **Management**

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

### **Question 8 of 148**

A 25-year-old woman is brought to the emergency department by ambulance after being found unwell by friends. Collateral history reported by the paramedics indicated that the patient had been unwell for 3 days with vomiting and diarrhoea. Her housemate said that the patient had been unable to eat since becoming unwell and that he did not think she had been taking her regular insulin during that time. The patient herself was too disorientated to give any history. The



paramedics had found both novorapid and lantus insulin pen devices in the patients fridge.

General examination indicated a drowsy and dehydrated patient with generalised abdominal tenderness but no evidence of focal peritonism.

Please see below for selected investigation results.

Observations: blood pressure 86 / 57 mmHg; heart rate 127 beats per minute; respiratory rate 28 per minute; O<sub>2</sub> saturations 100 % (room air); Temperature 37.1 oC.

Fingerpick blood glucose 38.2 mmol / L

Fingerpick blood ketones 8.7 mmol / L

Urea 12.5 mmol / L

Creatinine 123 micromol / L

Sodium 148 mmol / L

Potassium 3.7 mmol / L

Haemoglobin 156 g / dL

White cell count  $14.3 \times 10^3$  / microlitre

Neutrophils  $11.3 \times 10^3$  / microlitre

Platelets  $453 \times 10^3$  / microlitre

Arterial blood gas (room air)

pH 7.05

PaCO<sub>2</sub> 15 mmHg (reference 32-43)

PaO<sub>2</sub> 99 mmHg (reference 70-100)

Bicarbonate 12.3 mmol / L (reference 20.0-26.0)

Chloride 111 mmol / L (reference 99-108)

Lactate 7.5 mmol / L

What is the appropriate strategy for intravenous insulin treatment in this patient?

[Variable rate insulin infusion without initial bolus, converting to subcutaneous insulin once acidosis resolved9%](#)[Fixed rate insulin infusion without initial bolus, converting to subcutaneous insulin once patient is eating and drinking normally52%](#)[Fixed rate insulin infusion following initial bolus, converting to subcutaneous insulin once patient is eating and drinking normally22%](#)[Variable rate insulin infusion with initial bolus, converting to subcutaneous insulin once acidosis resolved10%](#)[Variable rate insulin infusion without initial bolus, converting to subcutaneous insulin once ketonaemia resolved7%](#)

The patient is presenting in diabetic ketoacidosis due to vomiting, dehydration and omission of prescribed insulin.

The Joint British Diabetes Society recommend an insulin infusion at rate 0.1 units / kg / h. An

initial bolus of insulin is not advised due to a randomised controlled trial that found no benefit. Fixed rate insulin infusions are now preferred over titration of insulin dose against blood sugar levels (sliding scale). This is due to the fact that blood glucose may correct more quickly than ketoacidosis and so ensures adequate insulin to eradicate ketones.

There is no consensus between expert bodies as to biochemical end-point of DKA, therefore it is advised that patients are transferred onto subcutaneous insulin once they are eating and drinking normally. It is vital to ensure an overlap between the administration of intravenous and subcutaneous insulin to avoid recurrent ketogenesis.

Misra S, Oliver N. Diabetic ketoacidosis in adults. BMJ 2015;351:h5660.

## **Diabetic ketoacidosis**

Diabetic ketoacidosis may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction

### **Features**

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

## **Diagnostic criteria**

### **American Diabetes Association (2009)**

#### **Key points**

- glucose > 13.8 mmol/l
- pH < 7.30
- serum bicarbonate < 18 mmol/l
- anion gap > 10
- ketonaemia

### **Joint British Diabetes Societies (2013)**

#### **Key points**

- glucose > 11 mmol/l or known diabetes mellitus
- pH < 7.3
- bicarbonate < 15 mmol/l
- ketones > 3 mmol/l or urine ketones ++ on dipstick

## Management

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia

### **JBDS example of fluid replacement regime for patient with a sSystolic BP on admission 90mmHg and over**

<b>Fluid</b>	<b>Volume</b>
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

### **JBDS potassium guidelines**

<b>Potassium level in first 24 hours (mmol/L)</b>	<b>Potassium replacement in mmol/L of infusion solution</b>
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

### **Complications of DKA and its treatment**

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema\*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

\* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

#### Question 9 of 148

A 19-year-old with type 1 diabetes presents to the Emergency Department feeling unwell. She states she has had vomiting and diarrhoea for 2 days and has not been taking her full insulin doses as she has been off her food. Her capillary glucose is 37 mmol/l and there are 4+ ketones on urinalysis.

An arterial blood gas is performed and the results are as follows:

pH 7.12  
pO<sub>2</sub> 13 kPa  
pCO<sub>2</sub> 3.5 kPa  
HCO<sub>3</sub> 13  
Na 129 mmol/l  
K 6.1 mmol/l

Which of the following is the most appropriate initial management?

[IV 0.9% NaCl bolus](#)[80%IV 10 units actrapid + 50ml 50% dextrose](#)[6%IV 8.4% sodium bicarbonate](#)[4%Empirical IV antibiotics](#)[4%Insulin sliding scale](#)[6%](#)

This is a classical presentation of diabetic ketoacidosis. While precise protocols vary, the key principals are initial fluid resuscitation with normal saline prior to starting an IV insulin infusion, and careful potassium replacement.

Low sodium is often seen and is a pseudohyponatraemia secondary to the high serum glucose.

Serum potassium derangements are common and need careful management. Potassium is driven into cells by insulin. Serum potassium levels are therefore often high on presentation while blood insulin levels are depleted. Despite this, total body potassium is low due to fluid losses and requires careful monitoring and replacement during treatment.

Source:

<http://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf>

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### **Question 1 of 138**

A 55-year-old male presented to his general practitioner with a 4-month history of sweating, fatigue and daytime tiredness. He attributed his tight rings to 'fluid retention' and has been experiencing worsening headaches and deterioration in his vision.

He was diagnosed with acromegaly and underwent surgery for this condition 1 month ago. He has been feeling well since and has not experienced any new symptoms.

Which of the following investigations would be most useful for monitoring the effect of his therapy?

[MRI pituitary 5% Echocardiography 4% Growth hormone levels 12% Insulin-like growth factor levels 62% Oral glucose tolerance test 16%](#)

Insulin-like growth factors (IGF-1) have a long half-life and so is a useful measurement to assess growth hormone secretion and therefore screen for acromegaly and monitor the response to therapy. Serum IGF-1 is the most feasible parameter to assess clinical disease activity, in everyday practice in the outpatient clinic setting. It is monitored every 6 months, and growth hormone (GH) levels are done yearly.

Note: Oral glucose tolerance test (plus GH levels) is not helpful for patients receiving somatostatin analogues, and for patients receiving GH receptor antagonist therapy, only IGF-1 should be measured.

### **Acromegaly: management**

Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

Dopamine agonists

- for example bromocriptine
- the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
- effective only in a minority of patients

Somatostatin analogue

- for example octreotide
- effective in 50-70% of patients
- may be used as an adjunct to surgery

Pegvisomant

- GH receptor antagonist - prevents dimerization of the GH receptor

- once daily s/c administration
- very effective - decreases IGF-1 levels in 90% of patients to normal
- doesn't reduce tumour volume therefore surgery still needed if mass effect

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

#### Question 2 of 138

A 19-year-old woman with a history of type 1 diabetes is brought to the Emergency department with nausea and vomiting. there is no history of diarrhoea. She also has coeliac disease. She follows a gluten free diet and takes a basal bolus insulin regime with a usual HbA1c of 53 mmol/mol. On examination her blood pressure is 100/80 mmHg with a postural drop of 20 mmHg. Pulse is 88 beats per minute and regular. She looks dehydrated and tanned, she puts her tan down to weeks in the garden after her exams.

#### Investigations

Hb	102 g/l	Na <sup>+</sup>	129 mmol/l
Platelets	189 * 10 <sup>9</sup> /l	K <sup>+</sup>	5.0 mmol/l
WBC	10.9 * 10 <sup>9</sup> /l	Urea	9.9 mmol/l
Neuts	6.2 * 10 <sup>9</sup> /l	Creatinine	113 µmol/l
Lymphs	1.1 * 10 <sup>9</sup> /l	CRP	42 mg/l
Eosin	1.5 * 10 <sup>9</sup> /l		

Which of the following is the most important intervention with respect to her management?

[Fluid restriction4%IV anti-emetic4%IV hydrocortisone77%IV normal saline11%NG feeding4%](#)

In a patient with type 1 diabetes, such tight glycaemic control with hypoglycaemia would be considered very unusual. Coupled with the easy tanning, nausea, vomiting, and postural drop in blood pressure, this is highly suggestive of possible Addison's disease. The slight rise in eosinophil count, anaemia, hyponatraemia and potassium at the upper end of the normal range, all support the diagnosis.

In this situation corticosteroid replacement is crucial, without it normal saline replacement alone won't correct any hypotension, nor will it improve hyponatraemia. Although anti-emetics and NG feeding may be useful in restoring this patient to health, they won't correct underlying adrenal insufficiency.



## **Addison's disease**

Autoimmune destruction of the adrenal glands is the commonest cause of primary hypoadrenalism in the UK, accounting for 80% of cases

### **Features**

- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases), vitiligo, loss of pubic hair in women, hypotension
- crisis: collapse, shock, pyrexia

## **Other causes of hypoadrenalism**

### **Primary causes**

- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

### **Secondary causes**

- pituitary disorders (e.g. tumours, irradiation, infiltration)

### **Exogenous glucocorticoid therapy**

## **Question 3 of 138**

A 47-year-old woman is admitted to the surgical ward with severe loin to groin abdominal pain. A CT-KUB reveals a right-sided renal calculus. When you clerk her in she admits to you that she has not felt herself for the past few weeks with polyuria, polydipsia, constipation and altered mood.

Blood tests show:

Estimated glomerular filtration rate >60 ml/min

Adjusted calcium	3.1 mmol/l (2.1-2.6 mmol/l)
Phosphate	0.6 mmol/l (0.8-1.4 mol/l)
Parathyroid hormone	5.1 pmol/l (1.2-5.8 pmol/l)

Which of the following is the most likely cause for her symptoms?

[Primary hyperparathyroidism63%](#)[Secondary hyperparathyroidism11%](#)[Sarcoidosis7%](#)[Tertiary hyperparathyroidism7%](#)[Type 1 renal tubular acidosis12%](#)

The most likely diagnosis here is primary hyperparathyroidism caused by parathyroid adenoma or hyperplasia. The classical biochemical findings are a high serum calcium and low phosphate. The parathyroid hormone level is either high or inappropriately normal.

Secondary hyperparathyroidism is caused by chronic hypocalcaemia (e.g. chronic kidney disease). Serum calcium is low or normal whilst parathyroid hormone levels are high.

Tertiary hyperparathyroidism develops from secondary hyperparathyroidism and results in autonomous parathyroid production. It is usually seen patients with end-stage renal disease.

Sarcoidosis and type 1 renal tubular acidosis are rare causes of hypercalcaemia.

## **Primary hyperparathyroidism**

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia

- 4%: multiple adenoma
- 1%: carcinoma

Features - 'bones, stones, abdominal groans and psychic moans'

- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture
- renal stones
- depression
- hypertension

Associations

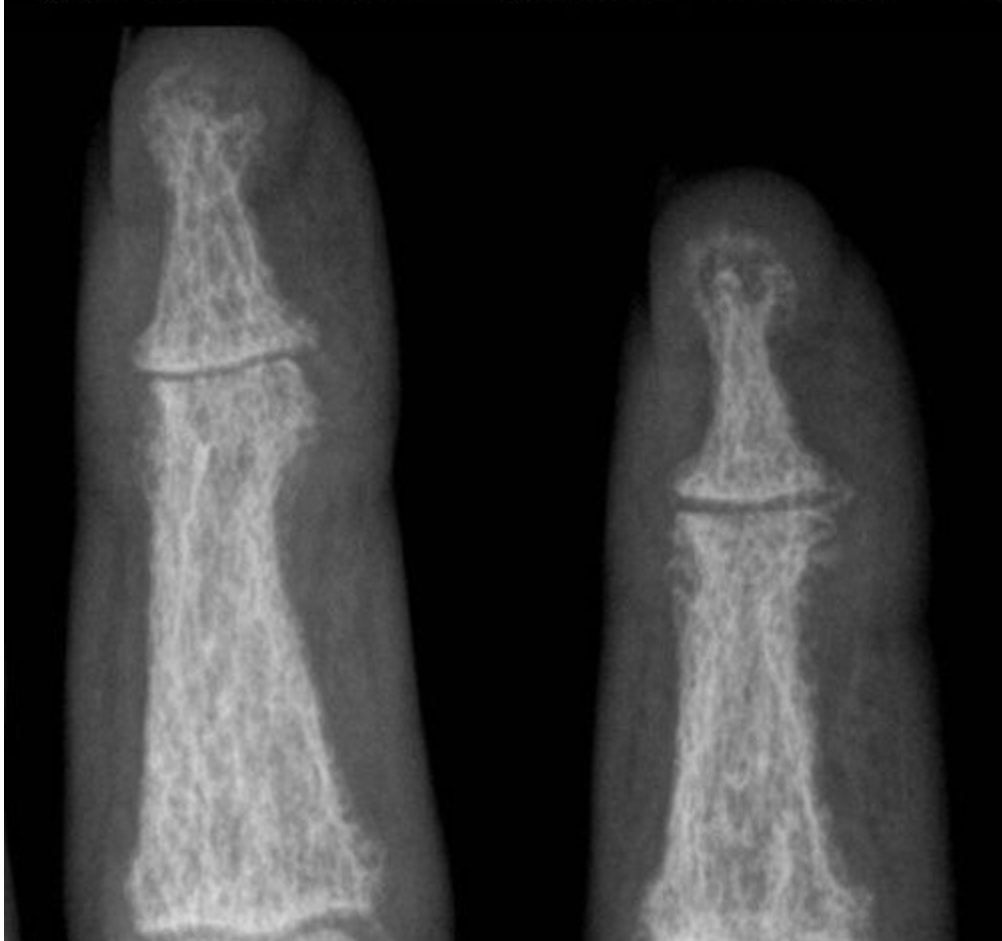
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- raised calcium, low phosphate
- PTH may be raised or normal
- technetium-MIBI subtraction scan

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- calcimimetic agents such as cinacalcet are sometimes used in patients who are unsuitable for surgery





Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

#### Question 4 of 138

A 19-year-old woman presents to the emergency department drowsy and vomiting. She is accompanied by a friend who tells you she has been out drinking all day and has been vomiting for the last few hours.

Her speech is slurred and confused, she opens her eyes in response to her name and pushes you away in response to a painful stimulus. Heart rate is 100 beats per minute and regular, blood pressure is 100/60 mmHg, capillary glucose is 18 mmol/L, and a urine dip shows pH: 4, blood: trace, ketones: +++, protein: trace, nitrites: negative and leukocytes: negative.

Chest x-ray: Normal

Venous blood gas:

pH 7.27 (7.35-7.45)

Bicarbonate 10mmol/L (22-26)

Base excess -10 (-2 to +2)

Sodium 135 mmol/L (137-144)

Potassium 2.9 mmol/L (3.5-4.9)

Chloride 99 mmol/L (95-107)

Serum Glucose: 21 mmol/L

What is the most important initial intervention?

[Fixed rate intravenous insulin infusion \(FRII\)10%](#)[Intravenous calcium gluconate4%](#)[Intravenous fluids77%](#)[Sliding scale insulin4%](#)[Urgent CT head4%](#)

This woman fits the diagnostic criteria for diabetic ketoacidosis (DKA):

- Ketonaemia > 3.0mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
- Blood glucose > 11.0mmol/L or known diabetes mellitus
- Bicarbonate ( $\text{HCO}_3^-$ ) < 15.0mmol/L and/or venous pH < 7.3

Diabetes UK guidance states that the most important initial therapeutic intervention in DKA is appropriate fluid replacement followed by insulin administration.

The key benefits of fluid resuscitation in this context include:

- Recovery of circulatory volume
- Clearance of ketones and therefore improvement of acidosis
- Correction of electrolyte imbalance

Weight based fixed rate intravenous insulin infusion (FRIII) is now the recommended mode of insulin administration in DKA, over sliding scale.

DKA is a complication of type i diabetes (but can rarely complicate type ii diabetes). It can be the first presentation of type i diabetes, result from poor diabetic control or be precipitated by another factor such as infection.

#### Question 7 of 138

A 19-year-old woman comes to the endocrine clinic for review. She has problems with hirsutism and irregular periods, and troublesome weight gain. Her GP has just stressed the need to lose weight and offered no pharmacological intervention. She takes no medication from the doctor and is currently studying law. Examination reveals a blood pressure of 135/85 mmHg, pulse is 65 beats per minute and regular. body mass index is 32kg/m<sup>2</sup>. You confirm extensive hirsutism affecting the beard line, upper lip and the nipples. there is acne over the face and the upper chest. Relevant bloods include:

testosterone 4.8 nmol/l (upper limit of normal 2.1 nmol/l)

LH:FSH ratio 2.1

fasting glucose 5.0 mmol/l

Her main concern is hirsutism.

Which of the following is the most appropriate intervention?

[Co-cyprindiol41%](#)[Clomiphene14%](#)[Levonorgestrel12%](#)[Metformin32%](#)[Pioglitazone1%](#)

Co-cyprindiol contains both cyproterone, an anti-androgen, and ethinylestradiol, (a synthetic oestrogen). In combination, used for the treatment of polycystic ovarian syndrome, the most likely diagnosis here, co-cyprindiol significantly reduces symptoms of hirsutism and acne, both related to androgen excess.

Clomiphene is the preferred option for inducing ovulation, and is preferred to metformin for this purpose, although the two are sometimes used in combination in the obese population.

Pioglitazone is also effective in reducing ovarian insulin resistance, and inducing ovulation, but

is not used due to its adverse event profile. Progesterone, (levonorgestrel), is ineffective in managing hirsutism.

## **Polycystic ovarian syndrome: management**

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

### **General**

- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

### **Hirsutism and acne**

- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

### **Infertility**

- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen\* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese

- gonadotrophins

\*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

#### Question 8 of 138

A 22-year-old female, who is known to have type 1 diabetes mellitus, presents with weight loss, anorexia and fatigue for the last six months.

Her diabetes was well controlled with soluble insulin three times daily and long acting insulin in the evening but during the last six months she noticed that her insulin requirement has generally decreased and on three occasions she had hypoglycaemic attacks.

During the same time period she had lost approximately 7 Kg in weight and had generally lost her appetite. She had also been amenorrhoeic over the last three months.

On examination, she is thin (BMI 18), with a pulse rate of 70 beats per minute and a blood pressure of 110/70 mmHg with a postural drop.

Investigations reveal:

Serum sodium	125mmol/L
Serum potassium	5.3mmol/L
Serum urea	7.4mmol/L
Serum creatinine	100 mol/L
Serum glucose	7.5mmol/L
HbA1c	6.0%
Serum free T4	7.5 pmol/L
Serum TSH	5.5 pmol/L
Serum oestradiol	70 pmol/L (130-850)
Serum LH	2.5 mU/L (2-10)
Serum FSH	2.2 mU/L (2-10)
Serum prolactin	400 mU/L (50-450)
Serum calcium	2.9 mmol/l
Serum phosphate	0.8 mmol/l

What is the most appropriate investigation for this patient?

[Thyroid autoantibodies5%PTH concentration8%Short synacthen test68%Pregnancy test9%Random cortisol concentration10%](#)



This known type 1 diabetic female has developed Addison's disease on top of her diabetes. This explains the hypoglycaemic attacks, the decrease in her insulin requirement, the fatigue and weight loss.

Both type 1 DM and Addison's disease are features of Schmidt's disease (type 2 autoimmune polyendocrine syndrome) which is the diagnosis in this case.

The low T4, raised TSH, high calcium, low FSH, low LH, low oestradiol (hypogonadotropic hypogonadism) are all features of Addison's disease.

The best investigation to diagnose Addison's disease is the short synacthen test.

It is of paramount importance when treating these patients is not to replace thyroxine before hydrocortisone because this will induce Addisonian crisis.

## **Addisonian crisis**

### **Causes**

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococemia)
- steroid withdrawal

### **Management**

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

### **Question 9 of 138**

A 40-year-old female presented to Endocrinology Clinic with a 3-month history of weight gain, fatigue and headaches. Over the last 3 weeks, she has also experienced galactorrhoea and

reduced libido. She was diagnosed with type 2 diabetes and hypertension 1 month ago and is on diet control for both. She is not currently on any regular medications. On examination, there was evidence of hirsutism and acne, a cervical fat pad, striae on her abdomen and proximal myopathy. Areas of hyperpigmentation were noted on her mucous membrane and palmar creases.

Which of the following investigations will reveal the diagnosis?

[Low dose dexamethasone suppression test31%](#)[Prolactin levels7%](#)[Urinary cortisol13%](#)[CT brain3%](#)[MRI pituitary45%](#)

The history suggests Cushing's syndrome, but the occurrence of galactorrhoea and reduced libido brings to attention the possibility of hyperprolactinaemia, and headaches may indicate an intracranial pathology. The diagnosis of a secreting pituitary tumour causing a raised level of prolactin and ACTH (causing hyperpigmentation) and hence, cortisol, should be suspected.

Low dose dexamethasone suppression test and 24-hour urinary cortisol will aid confirming the presence of Cushing's syndrome. Raised prolactin levels will confirm hyperprolactinaemia, however, it is the MRI pituitary that will lead to the diagnosis of a pituitary tumour.

## **Pituitary tumours**

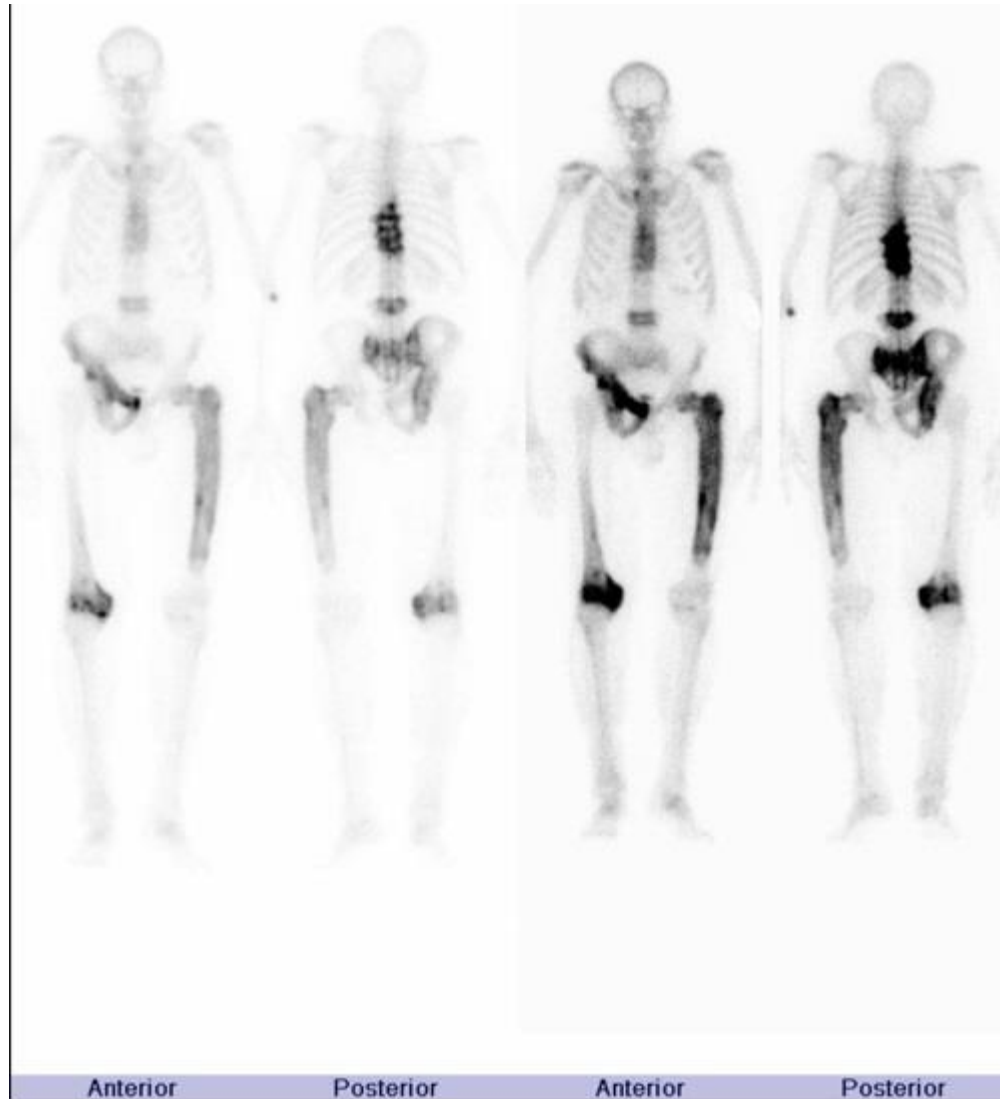
Hormones secreted

- prolactin- 35%
- no obvious hormone, 'non-functioning', 'chromophobe' - 30%
- growth hormone - 20%
- prolactin and growth hormone - 7%
- ACTH - 7%
- others: TSH, LH, FSH - 1%

Question 10 of 138

A 76-year-old is investigated for persistent and progressive pain in his back and left hip. This is no longer responding to standard analgesia and has resulted in him taking regular modified-release morphine sulphate. Standard plain films of his left hip did not show changes consistent with osteoarthritis.

An isotope bone scan is therefore ordered to investigate his pain further:



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What is the most likely cause of his pain?

[Multiple myeloma12%](#)[Metastatic prostate cancer16%](#)[Paget's disease of the bone65%](#)[Osteoporosis4%](#)[Ankylosing spondylitis3%](#)

The bone scan demonstrates intense uptake involving several lower thoracic vertebrae, L3, right hemipelvis, sacrum, left proximal femur and right knee. There is expansion and bowing of the involved femur. These changes are typical of Paget's disease.

Isotope bone scans are not useful for assessing multiple myeloma or osteoporosis.

## **Paget's disease of the bone**

Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

### Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

### Clinical features - only 5% of patients are symptomatic

- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium\* and phosphate are typically normal
- skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's

- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

### Complications

- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



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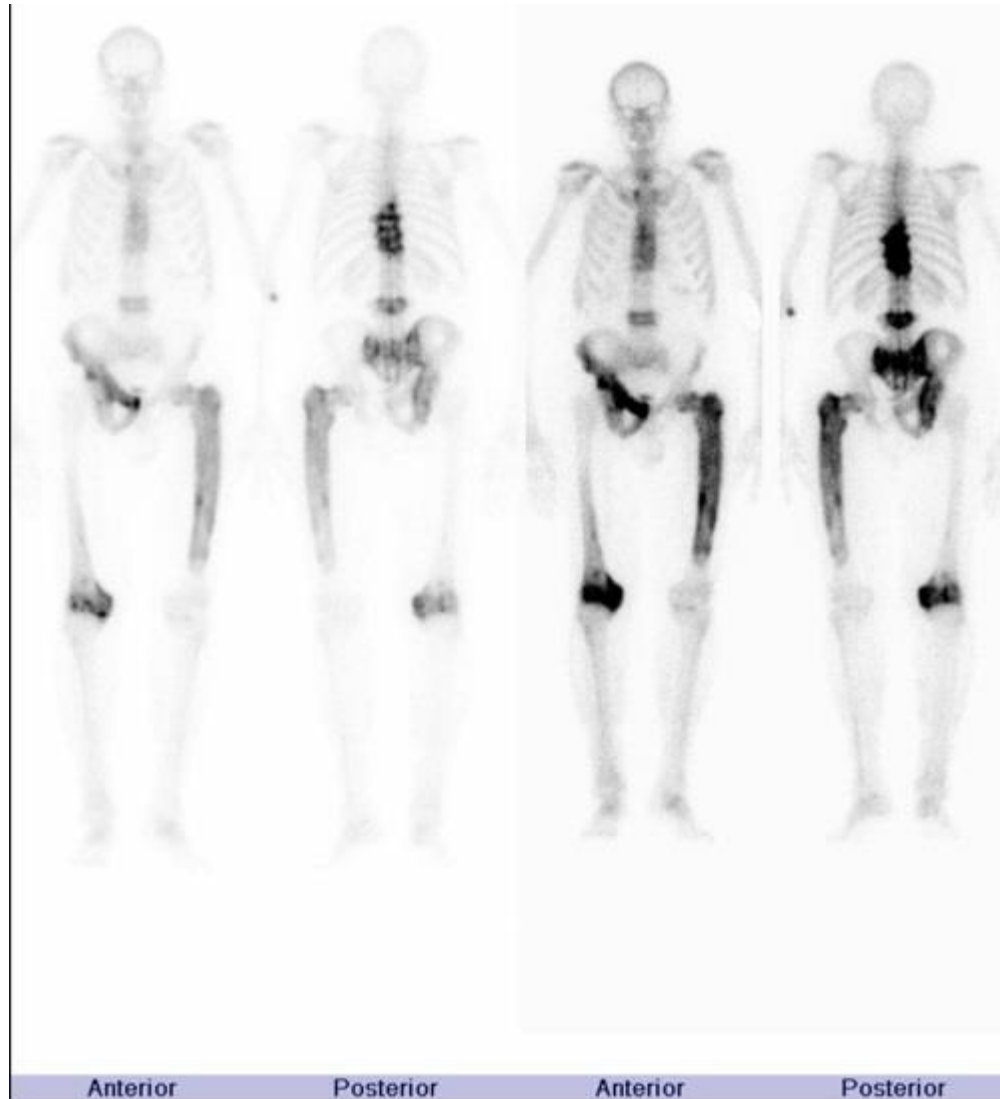
The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.



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Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.



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Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilization

### Question 1 of 128

A 28-year-old woman has presented with a 5 month history of weight loss (despite an increase in appetite), tremor, loose bowels, and heat intolerance. She has otherwise been well and her only significant family history is that her brother has alopecia areata. She tells you that she had a positive pregnancy test last week and is awaiting her booking appointment. On examination, she appears anxious and her heart rate is 105 beats/minute. She has a tremor when her arms are outstretched and her eyes appear large. She also has a goitre. The rest of her examination is unremarkable. Her blood results find hyperthyroidism. Which of the following medications are most suited to treat her hyperthyroidism?

[Propylthiouracil63%](#)[Carbimazole18%](#)[Radioactive iodine6%](#)[Carbimazole and Levothyroxine9%](#)[Levothyroxine5%](#)

During early pregnancy, propylthiouracil should be used. The block and replace strategy is not advised as it can lead to problems in the fetus and radioactive iodine is contraindicated. Please see the link below for more information:

<https://www.evidence.nhs.uk/formulary/bnf/current/6-endocrine-system/62-thyroid-and-antithyroid-drugs/622-antithyroid-drugs>

### **Pregnancy: thyroid problems**

In pregnancy there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level

### **Thyrotoxicosis**

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in second and third trimester

### **Management**

- propylthiouracil has traditionally been the antithyroid drug of choice. This approach was supported by the 2007 Endocrine Society consensus guidelines
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism



- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation  
- helps to determine risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

## Hypothyroidism

### Key points

- thyroxine is safe during pregnancy
- serum thyroid stimulating hormone measured in each trimester and 6-8 weeks post-partum
- some women require an increased dose of thyroxine during pregnancy
- breast feeding is safe whilst on thyroxine

### Question 3 of 128

A 45-year-old lady is admitted to hospital with abdominal pain and malaise. She has no past medical history and takes no regular medications or supplements. Bloods tests show:

Ca  $2^{++}$  2.70 mmol/l

PO $4^{+}$  1.2 mmol/l

Creatinine 60  $\mu$ mol/l

Chest X-ray - normal appearances

She denies taking any medications or supplements. Her chest X-ray is normal in appearance, and renal function normal. You ring the GP and find out her calcium was also slightly raised 8 years ago. What is the most likely diagnosis?

[Secondary hyperparathyroidism 7%](#) [Malignancy with bony metastasis 5%](#) [Primary hyperparathyroidism 34%](#) [Familial hypocalciuric hypercalcaemia 48%](#) [Sarcoidosis 6%](#)

PO $4$  would normally be low in primary hyperparathyroidism. Her renal function is normal excluding secondary hyperparathyroidism. Sarcoidosis is unlikely with a normal CXR. This leaves malignancy or familial hypocalciuric hypercalcaemia. Although malignancy is possible her raised Ca $^{2+}$  8 years makes familial hypocalciuric hypercalcaemia more likely.

## **Familial benign hypocalciuric hypercalcaemia**

Familial benign hypocalciuric hypercalcaemia is a rare autosomal dominant disorder characterised by asymptomatic hypercalcaemia. It is due to a defect in the calcium-sensing receptor and a decreased sensitivity to increases in extracellular calcium.

The parathyroid hormone level is often not suppressed, as would be expected in all non-hyperparathyroidism related cases of hypercalcaemia. This is due to the decreased sensitivity to increases in extracellular calcium.

Question 4 of 128

A 27-year-old woman who is 11 weeks pregnant comes for review. This is her second pregnancy. During her first pregnancy she was diagnosed with gestational diabetes which resolved following the birth of her son. What is the most appropriate management at this stage?

[Perform an oral glucose tolerance test68% Advise on a diabetic diet and start metformin at 20 weeks6% Arrange a fasting glucose13% Arrange a HbA1c test6% Advise on a diabetic diet and start insulin at 20 weeks7%](#)

The oral glucose tolerance test remains the investigation of choice for gestational diabetes

## **Pregnancy: diabetes mellitus**

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates around 1 in 40 pregnancies. NICE updated the guidance in 2015

Risk factors for gestational diabetes

- BMI of  $> 30 \text{ kg/m}^2$
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- women who've previously had gestational diabetes: oral glucose tolerance test (OGTT) should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

#### Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is  $\geq 5.6$  mmol/l
- 2-hour glucose is  $\geq 7.8$  mmol/l

#### Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about selfmonitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is  $< 7$  mmol/l a trial of diet and exercise should be offered
- if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
- if glucose targets are still not met insulin should be added to diet/exercise/metformin
- if at the time of diagnosis the fasting glucose level is  $\geq 7$  mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

#### Management of pre-existing diabetes

- weight loss for women with BMI of  $> 27$  kg/m<sup>2</sup>
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

### Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

#### Question 6 of 128

A 47-year-old builder presented with paraesthesia in both hands which was worse at night. His hands felt swollen, although they were not painful, and he had needed to buy a larger pair of work gloves. When at work he found that his hands felt weak. Over the past six months he had been experiencing urinary frequency, fatigue and increased thirst.

He had a past medical history of obesity and hypertension and his brother had type II diabetes mellitus. His only medication was ramipril. He was a heavy smoker with a 20 pack year history.

On examination of the arms there was weakness of thumb abduction bilaterally and diminished sensation over the radial three and a half digits. Percussion over the palmar aspect of the wrist reproduced the paraesthesia he described on presentation. On examination of the chest and abdomen there were areas of pigmentation in both axillae and striae over the abdomen. He had a protruberent abdomen and an elevated body mass index (BMI).

Which of the following investigations is most likely to be diagnostic?

[Magnetic Resonance Imaging of the Pituitary and visual field testing](#)17%[Fasting glucose on three occasions, glycosylated haemoglobin \(HbA1c\) and a 9am cortisol measurement](#)8%[Growth hormone measurement and dexamethasone suppression test](#)11%[Nerve conduction studies and electromyogram \(EMG\)](#)6%[Oral glucose tolerance test with serum glucose, IGF-1 and growth hormone measurements](#)57%

This gentleman has bilateral carpal tunnel syndrome with an underlying diagnosis of acromegaly.

The features in the question which point to the diagnosis of acromegaly include the presence of a recent increase in hand size and known complications of acromegaly such as diabetes mellitus (polyuria and polydipsia), acanthosis nigricans (pigmentation in the axillae) and carpal tunnel syndrome.

The increased BMI and striae could be indicative of underlying Cushing's disease but in this case these were red herrings.

The diagnosis of acromegaly is made when there is a failure to suppress the release of growth hormone during an oral glucose tolerance test. This test also allows the diagnosis of diabetes mellitus to be made. Due to the diurnal variation in growth hormone levels, a random measurement is not helpful in making a diagnosis.

Although an MRI scan of the pituitary and visual field testing are very important investigations and can confirm the presence of a pituitary adenoma they will confirm or exclude a diagnosis of acromegaly.

A fasting glucose and HbA1c measurement may aid the diagnosis of diabetes mellitus but not acromegaly.

A 9am cortisol and dexamethasone suppression test could be used to investigate Cushing's syndrome and therefore are not relevant here.

Nerve conduction studies and electromyography would confirm the diagnosis of carpal tunnel syndrome but the underlying cause i.e. acromegaly.

### **Acromegaly: investigations**

Growth hormone (GH) levels vary during the day and are therefore not diagnostic. The definitive test is the oral glucose tolerance (OGTT) with serial GH measurements. Serum IGF-1 may also be used as a screening test and is sometimes used to monitor disease.

Oral glucose tolerance test

- in normal patients GH is suppressed to  $< 2 \text{ mu/L}$  with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour

A 42-year-old woman was seen in Endocrinology Clinic with a 4-month history of amenorrhoea. On questioning, she reports having to wax her arms and upper lip. Her mother went through early menopause at 28 after having an emergency hysterectomy post-partum. On examination, her body mass index is 38 kg/m<sup>2</sup> but otherwise unremarkable.

Her GP has kindly ordered blood tests prior to her appointment

#### Investigations

LH	40 IU/L (5 to 25 IU/L)
FSH	8 IU/ (1 to 11 IU/L)
Estradiol	720 pmol/L (70-500 pmol/L)
Progesterone	220 nmol/L (35-92 nmol/L)
Thyroid Stimulating Hormone	5.6 mIU/L (0.5 -6.0 mIU/L)
Prolactin	700 mIU/L (105-548mIU/L)

What is the most likely diagnosis?

[Prolactinoma10%Polycystic Ovarian Syndrome40%Premature Ovarian Failure  
13%Pregnancy31%Subclinical Hypothyroidism6%](#)

The most likely diagnosis is pregnancy. The elevated estradiol and progesterone are characteristic with a slight rise in the LH level.

The prolactin level is only mildly elevated so a prolactinoma is unlikely especially with the rise in other hormone levels. Polycystic ovarian syndrome is associated with androgen excess and an elevated LH to FSH ratio. While androgen (testosterone) hasn't been measured, it is not associated with rises in estradiol or progesterone.

Premature Ovarian Failure typically presents with low levels of estradiol and a raised FSH level. Subclinical hypothyroidism is linked with oligo-ovulation but in this case, the TSH level is normal excluding this as a diagnosis

#### **Pregnancy: physiological changes - endocrine**

##### Progesterone

- during the first 2 weeks stimulates the fallopian tubes to secrete the nutrients the zygote/blastocyst requires
- placenta starts production at 6 weeks and takes over at 12 weeks

- progesterone inhibits uterine contractions by

1. Inhibiting production of prostaglandins

2. Decreasing sensitivity to oxytocin

- stimulates development of lobules and alveoli

## Oestrogen

- oestriol is major oestrogen (not oestradiol)
- stimulates the continued growth of the myometrium
- stimulates the growth of the ductal system of the breasts

## Prolactin

- increase during pregnancy probably due to oestrogen rise
- initiates and maintains milk secretion of the mammary gland
- essential for the expression of the mammatropic effects of oestrogen and progesterone
- oestrogen and progesterone directly antagonises the stimulating effects of prolactin on milk synthesis

## hCG

- secreted by syncytiotrophoblast, stimulated by GnRH produced in adjacent cytotrophoblast
- can be detected within 9 days, peak secretion at 9 weeks
- mimics LH, thus rescuing the corpus luteum from degenerating and ensuring early oestrogen and progesterone secretion
- stimulates production of relaxin
- may inhibit contractions induced by oxytocin

## Also

- Relaxin: suppresses myometrial contractions and relaxes the pelvic ligaments and pubic symphysis
- hPL: has lactogenic actions (insignificant with respect to prolactin) - antagonises insulin, therefore making less glucose available to the mother - enhances protein metabolism

### Question 8 of 128

A 19-year-old pharmacy student is admitted to hospital after collapsing while at work. She denies biting her tongue or becoming incontinent during the collapse and was groggy but alert on coming around. At the time, a first aider measured her blood glucose to be 1.5 mmol/l. The patient's mother reports that the patient has had 2 other episodes of collapse.

The student's observations include a blood pressure of 127/77 mmHg, pulse of 81 bpm, and oxygen saturation of 97%.

What is the best first-line investigation?

[Glucose, c-peptide and insulin79%](#) [Morning c-peptide8%](#) [Evening c-peptide4%](#) [Computed tomography \(CT\) scan of the abdomen4%](#) [Oral glucose tolerance test4%](#)

Measuring blood glucose, insulin and c-peptide allows the differentiation between the causes of hypoglycaemic attacks, including insulinoma, insulin or sulphonylurea misuse.

## Hypoglycaemia

### Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol

### Other possible causes in children

- nesidioblastosis - beta cell hyperplasia



A 40 year old man presents to the Emergency Department with tiredness and dizziness (worse on standing) which has been ongoing for the past few months. He had a past medical history of epilepsy and mentions that he has had 'brain surgery' in the past. He is on some medications but cannot remember the names. He has no allergies.

On assessment, he has no focal neurological deficit and cardiovascular/respiratory examination is normal. Observations show a blood pressure of 135/90 mmHg (dropping to 105/82 mmHg on standing), a heart rate of 67 beats per minute, a temperature of 36.2 degrees, oxygen saturations of 94% on air and a respiratory rate of 18/min. Given his medical history, you opt to keep this gentleman in the short stay unit for observation overnight.

Baseline blood tests are as follows:

Hb 125 g/l  
WCC  $9.2 \times 10^9/l$   
Plt  $290 \times 10^9/l$   
CRP 10 mg/l  
Gluc 3.9 mmol/l  
Na<sup>+</sup> 138 mmol/l  
K<sup>+</sup> 5.8 mmol/l  
Ur 7.2 mmol/l  
Cr 100  $\mu$ mol/l  
TSH 0.4 mU/l  
T4 5.0 pmol/l

Given the above, what is the most likely underlying diagnosis?

[Hypopituitarism70% Hypothyroidism5% Acromegaly6% Pheochromocytoma6% Medication side effects13%](#)

This gentleman has hypopituitarism following 'brain surgery'. Though the details of this are obscured in the question, it is likely that removal of a pituitary mass with trans-sphenoidal surgery. This is exhibited by fairly non-descript symptoms coupled with some underlying evidence of lack of anterior pituitary hormones: low BP/dizziness/postural hypotension, high/normal K<sup>+</sup>, low/normal Na<sup>+</sup> and low/normal blood glucose all indicate lack of cortisol due to low ACTH; the low/normal temperature and heart rate and the tiredness steer you towards low thyroxine level due to lack of TSH.

This gentleman needs assessment of his pituitary function. This can be done in many ways. A baseline pituitary hormone profile can be quite useful; however the most definitive tests involve assessing dynamic pituitary function. The insulin stress test (coupled with TRH and GnRH tests) creates a hypoglycaemic effect in the body and the response of the pituitary (cortisol surge) is measured. However, inducing hypoglycaemia in epileptics, such as this gentleman, is contraindicated. Therefore the next best investigation is the glucagon stimulation test which

mimics hypoglycaemia in the body and causes a fake stress on the pituitary, therefore being safe to use in epileptics.

## **Hypopituitarism**

Adult growth hormone deficiency

- low peak growth hormone levels in response to insulin-induced hypoglycaemia

Features - mix

- low ACTH: tiredness, postural hypotension
- low gonadotrophins: amenorrhoea
- low TSH: constipated

Question 2 of 118

You review a 68-year-old patient in the diabetic clinic. He was diagnosed 28 years ago with type 2 diabetes and over this time has been through a number of antiglycemic agents including biguanides, sulfonylureas, thiazolidinediones and insulin. He is generally well but reports painless macroscopic haematuria and would like to be referred to a urologist as he has read about bladder cancer associated with one of his medications.

Which of the following antiglycemic agents can cause bladder cancer?

[Gliclazide5% Tolbutamide19% Pioglitazone65% Insulin detemir4% Sitagliptin8%](#)

Answer: Pioglitazone

Pioglitazone has been associated with an increased risk of bladder cancer. The greatest risk was shown in those patients who have used pioglitazone long term.

Risk of Bladder Cancer Among Diabetic Patients Treated With Pioglitazone Interim report of a longitudinal cohort study <http://care.diabetesjournals.org/content/34/4/916>

## Thiazolidinediones

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

### Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

### Question 4 of 118

A 54-year-old man presents to the diabetes clinic for review. He has had symptoms of polyuria, polydipsia and lethargy over the past few months, and his fasting glucose is elevated at 7.6 mmol/l. He has no history of diabetes in his family and is currently treated for hypertension and dyslipidaemia by his GP. On examination his blood pressure is 155/90 mmHg, pulse is 70 beats per minute and regular. His body mass index is 34 kg/m<sup>2</sup>. Other blood tests of note include GAD+ antibodies, renal function is normal.

Which of the following is most appropriate with respect to managing his glucose control?

[Gliclazide12%Liraglutide6%Metformin55%Sitagliptin4%Basal bolus insulin22%](#)

Up to 10% of patients who are thought to have type 2 diabetes are found to also be GAD autoantibody positive. These individuals are thought to progress faster to insulin start than patients with autoantibody negative type 2 diabetes, (within 3-5 years vs 7 years on average for 'standard' patients).

The management of these patients is the same as for patients with autoantibody negative disease,

metformin as the initial therapy of choice. Weight reduction may delay progression to insulin, therefore insulin sparing strategies, at least during the first few years after diagnosis are the preferred intervention. These may include use of SGLT-2 inhibitors or GLP-1 agonists.

Diapedia reference:

<http://www.diapedia.org/type-1-diabetes-mellitus/2104458121/lada-latent-autoimmune-diabetes-of-the-adult>

#### Question 5 of 118

A 78-year-old female attends the diabetes clinic. She has longstanding type 2 diabetes. Over the last few years she has become increasingly frail. Her main complaint is recurrent nausea and vomiting. Earlier this year she underwent endoscopy and gastric emptying studies which confirmed gastroparesis. She has since been started on metoclopramide which has had minimal effect on her symptoms. Her weight has decreased by 10% over the past year with a current BMI of 26 kg/m<sup>2</sup>.

Her HbA1c today at the clinic is 44 IFCC mmol/l (6.2%) having been 60 IFCC mmol/l (7.6%) this time last year.

Her past medical history includes chronic kidney disease stage 3 and aortic stenosis.

Her current therapy is Humulin M3 22 units at breakfast and dinner, metformin 500mg BD, ramipril 5mg OD, bendroflumethiazide 2.5mg OD, aspirin 75 mg OD.

She lives alone and is still driving. She denies the need for carers, however, she has had 3 falls in the past month. She describes particular difficulty getting up in the morning and says her mood can often be low in the mornings.

She checks her blood sugar once daily in the morning with the following results.

Saturday	3.1 mmol/l
Sunday	4.0 mmol/l
Monday	4.1 mmol/l
Tuesday	3.2 mmol/l
Wednesday	14.6 mmol/l
Thursday	3.5 mmol/l
Friday	16.1 mmol/l

What is the correct step in the management of her diabetes?

[Change Humulin M3 to a glucagon-like-peptide 1 receptor agonist16%Stop metformin 10%Add sitagliptin6%Change Humulin M3 to 20 units in the morning and 10 units in the evening59%Change Humulin M3 to 30 units once daily9%](#)

This lady's fasting blood sugars are too low. The 2 high readings raise the concern of overnight hypoglycaemia with reflex hyperglycaemia in the morning. Her recent weight loss will mean her insulin resistance will have decreased (as reflected in her decreasing HbA1c) and she will require smaller doses of insulin. Changing her insulin from a total of 44 units daily to 30 units daily offers protection against hypoglycaemia. Furthermore altering her split of insulin to the conventional 2/3rd in the morning and 1/3rd in the evening reduces the risk of overnight hypos.

The risks of tight glycaemic control in this lady vastly outweigh any benefits. She should be advised to check her sugar more regularly for the short-term and given advice regarding driving. Close follow-up with the diabetic nurses should be arranged until her hypo risk is reduced.

There is no indication for a GLP1 agonist (BMI 26) and metformin should continue (assuming eGFR remains above 30) to allow the reduction in her insulin doses to lowest effective levels.

## **Insulin therapy: side-effects**

### Hypoglycaemia

- patients should be taught the signs of hypoglycaemia: sweating, anxiety, blurred vision, confusion, aggression
- conscious patients should take 10-20g of a short-acting carbohydrate (e.g. a glass of Lucozade or non-diet drink, three or more glucose tablets, glucose gel)
- every person treated with insulin should have a glucagon kit for emergencies where the patient is not able to orally ingest a short-acting carbohydrate
- patients who have frequent hypoglycaemic episodes may develop reduced awareness. If this develops then allowing glycaemic control to slip for a period of time may restore their awareness
- beta-blockers reduce hypoglycaemic awareness

### Lipodystrophy

- typically presents as atrophy of the subcutaneous fat
- can be prevented by rotating the injection site

### Question 6 of 118

You are asked to review a 43-year-old man in theatre recovery who has developed a fever and tachycardia post-operatively. He is previously fit and well, does not smoke and drinks alcohol only occasionally. He had fallen the previous night and suffered a distal radius fracture and has just undergone an open reduction and internal fixation under general anaesthetic. During anaesthesia he received 4mg ondansetron and 8mg dexamethasone for post-operative nausea and 10mg morphine for pain. He denies feeling unwell and has no symptoms suggestive of intercurrent infection.

On examination his heart rate is 130 beats/min and irregular, his blood pressure is 135/74 mmHg and his temperature is 39.4°C. His chest is clear to auscultation, his abdomen soft and non-tender and there is no rash or meningism. His right forearm is in plaster, but is not particularly painful and his fingers are warm and have normal sensation.

Hb	130 g/l
Platelets	460 * 10 <sup>9</sup> /l
WBC	10.5 * 10 <sup>9</sup> /l
Na <sup>+</sup>	138 mmol/l
K <sup>+</sup>	4.1 mmol/l
Urea	5.1 mmol/l
Creatinine	95 µmol/l
C-reactive protein	1 mg/L
Thyroid stimulating hormone	<0.02 mIU/L
Cortisol	45 µg/dL

What is the most appropriate initial treatment?

[Carbimazole 10%](#) [Hydrocortisone 28%](#) [Propranolol 42%](#) [Broad spectrum antibiotics 8%](#) [Crystalloid infusion 11%](#)

The diagnosis here is thyrotoxicosis as a presenting feature of hyperthyroidism. Infection is unlikely given the normal clinical examination and normal CRP. During initial treatment of thyrotoxicosis it is important to treat hypoadrenalism first - if present - in order to not precipitate an Addisonian crisis. However, this patient has no features in the history to suggest pre-existing Addison's disease, he has normal electrolytes and the suppressed cortisol can be explained by the peri-operative use of dexamethasone. Initial treatment of thyrotoxicosis should focus on sympathetic storm suppression using beta blockade. Anti-thyroid medications - i.e. carbimazole - take up to six weeks to take full effect and are not useful in the acute scenario.

## Thyrotoxicosis

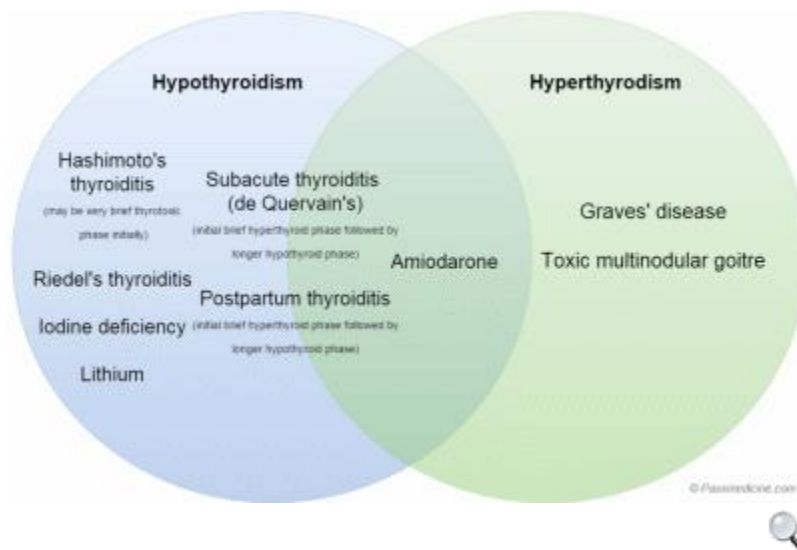
Graves' disease accounts for around 50-60% of cases of thyrotoxicosis.

### Causes

- Graves' disease
- toxic nodular goitre
- acute phase of subacute (de Quervain's) thyroiditis
- acute phase of post-partum thyroiditis
- acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- amiodarone therapy

### Investigation

- TSH down, T4 and T3 up
- thyroid autoantibodies
- other investigations are not routinely done but includes isotope scanning



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase

### Question 7 of 118

A 70-year-old woman is reviewed in the chronic kidney disease clinic. She also has a history of hypertension for which she takes amlodipine 5mg od and ramipril 10mg od. Her most recent results are as follows:

Blood pressure today is 128/74 mmHg.

	Recent	12 months ago
Na <sup>+</sup>	140 mmol/l	141 mmol/l
K <sup>+</sup>	4.5 mmol/l	4.3 mmol/l
Urea	11.2 mmol/l	10.5 mmol/l
Creatinine	124 µmol/l	114 µmol/l
eGFR	39 ml/min	43 ml/min

What is the most appropriate next step in management?

[Start atorvastatin 20mg on 42%](#)[Reduce ramipril to 5mg od and recheck U&Es in 4 weeks 13%](#)[Start simvastatin 40mg on 5%](#)[Increase amlodipine to 10mg od 5%](#)[Check her QRISK2 score 34%](#)

QRISK2 should not be used in patients with chronic kidney disease (CKD). NICE now recommends that all patients with CKD should take a statin.

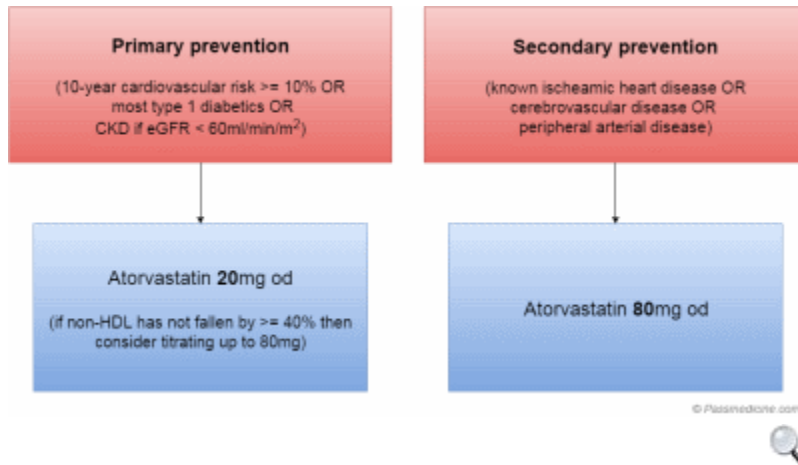
*Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD*

- *Increase the dose if a greater than 40% reduction in nonHDL cholesterol is not achieved and eGFR is 30 ml/min*
- *Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min*

### Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.





Graphic showing choice of statin.

### Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged ≤ 84 years. Patients ≥ 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

### Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checking to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples does not need to be fasting.

In the vast majority of patient the cholesterol measurements will be fed into the QRISK2 tool. If however the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if the total cholesterol concentration is  $> 7.5$  mmol/l and there is a family history of premature coronary heart disease. They also recommend referring people with a total cholesterol  $> 9.0$  mmol/l or a non-HDL cholesterol (i.e. LDL) of  $> 7.5$  mmol/l even in the absence of a first-degree family history of premature coronary heart disease.

### **Interpreting the QRISK2 result**

Probably the headline changes in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

**NICE now recommend we offer a statin to people with a QRISK2 10-year risk of  $\geq 10\%$**

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

### **Special situations**

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - $\rightarrow$  older than 40 years, or
  - $\rightarrow$  have had diabetes for more than 10 years or
  - $\rightarrow$  have established nephropathy or
  - $\rightarrow$  have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR  $> 30$  ml/min. If the eGFR is  $< 30$  ml/min a renal specialist should be consulted before increasing the dose

### **Secondary prevention**

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

### **Follow-up of people started on statins**

NICE recommend we follow-up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

### **Lifestyle modifications**

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be  $\leq 30\%$  of total energy intake
- saturated fats should be  $\leq 7\%$  of total energy intake
- intake of dietary cholesterol should be  $< 300$  mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do musclestrengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

## Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

## Alcohol intake

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

## Smoking cessation

- smokers should be encouraged to quit

## Question 8 of 118

A 22-year-old Asian woman with a body mass index of 24 kg/m<sup>2</sup> presents with new onset acne, hirsutism, and weight gain. Upon further questioning, it is found that she has had irregular periods for the last two years. On examination, there is mild acne and thick hair growth on her chin and areola region. Abdominal exam is unremarkable.

What are the most likely biochemical results given the clinical findings?

[Raised testosterone, low LH/FSH ratio, insulin resistance23%](#)  
[Low testosterone, low LH/FSH ratio, insulin resistance4%](#)  
[Low testosterone, raised LH/FSH ratio, insulin resistance6%](#)  
[Raised testosterone, raised LH/FSH ratio, increased insulin sensitivity6%](#)  
[Raised testosterone, raised LH/FSH ratio, insulin resistance61%](#)

The clinical description is consistent with polycystic ovary syndrome (PCOS). This presents with hirsutism, acne, oligo/amenorrhoea and subfertility. Biochemical findings in PCOS include insulin resistance, raised testosterone, raised LH/FSH ratio, raised prolactin and low HDL.

## Polycystic ovarian syndrome: features and investigation

Polycystic ovary syndrome (PCOS) is a complex condition of ovarian dysfunction thought to

affect between 5-20% of women of reproductive age. The aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

### Features

- subfertility and infertility
- menstrual disturbances: oligomenorrhea and amenorrhoea
- hirsutism, acne (due to hyperandrogenism)
- obesity
- acanthosis nigricans (due to insulin resistance)

### Investigations

- pelvic ultrasound: multiple cysts on the ovaries
- FSH, LH, prolactin, TSH, and testosterone are useful investigations: raised LH:FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis. Prolactin may be normal or mildly elevated. Testosterone may be normal or mildly elevated - however, if markedly raised consider other causes
- check for impaired glucose tolerance

### Question 9 of 118

A 37-year-old woman is referred by her GP after complaining of a swelling on the anterior aspect of her neck. On examination she is found to have a 2 cm nodule on the thyroid gland that moves on swallowing.

She has a past medical history of anxiety/depression and currently takes sertaline 100mg od. Her mother was diagnosed as having hypothyroidism in her 60's.

Thyroid functions tests are shown below:

Free T4 14 pmol/l

TSH 2.6 mu/l

A fine needle aspiration of the mass is consistent with papillary thyroid cancer. There is no current evidence of metastases. What is the most appropriate treatment?

[Total thyroidectomy followed by radioiodine-131 50% Localised radiotherapy 5% Total thyroidectomy 18% Total thyroidectomy followed by localised radiotherapy 22% Radioiodine-131 15%](#)

## Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

### Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

### Further information

Type	Notes
Papillary carcinoma	<ul style="list-style-type: none"><li>• Usually contain a mixture of papillary and colloidal filled follicles</li><li>• Histologically tumour has papillary projections and pale empty nuclei</li><li>• Seldom encapsulated</li><li>• Lymph node metastasis predominate</li><li>• Haematogenous metastasis rare</li></ul>
Follicular adenoma	<ul style="list-style-type: none"><li>• Usually present as a solitary thyroid nodule</li><li>• Malignancy can only be excluded on formal histological assessment</li></ul>
Follicular carcinoma	<ul style="list-style-type: none"><li>• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.</li><li>• Vascular invasion predominates</li></ul>

Type	Notes
Medullary carcinoma	<ul style="list-style-type: none"> <li>• Multifocal disease rare</li> <li>• C cells derived from neural crest and not thyroid tissue</li> <li>• Serum calcitonin levels often raised</li> <li>• Familial genetic disease accounts for up to 20% cases</li> <li>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.</li> </ul>
Anaplastic carcinoma	<ul style="list-style-type: none"> <li>• Most common in elderly females</li> <li>• Local invasion is a common feature</li> <li>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.</li> </ul>

#### Question 1 of 108

A 15-year-old girl was seen in clinic with lethargy, weakness worsening over the past 4 weeks. She also complains of recurrent muscle cramps in her legs, causing her to have trouble sleeping. On further questioning she admits to urinary frequency, passing urine up to ten times a day, and feels dehydrated all the time. She has also previously been diagnosed with cyclical vomiting syndrome and vomits 2-3 times a week.

On examination, she is thin, with a body mass index of 17.5kg/m<sup>2</sup>. Her heart rate is 89 bpm and blood pressure is 103/76 mmHg.

The results of the investigations at the clinic are as follow:

C Reactive protein	3 mg/l
Haemoglobin	158 g/l
White cell count	7.6 x 10 <sup>9</sup> /L
Na+	136 mmol/l
K+	2.9 mmol/l
Urea	7.2 mmol/l
Creatinine	108 µmol/l
Corrected calcium	2.42 mmol/l
Serum renin levels	8.6 ng/ml/hr
Serum aldosterone levels	750 ng/l
Urine chloride levels	90 mmol/l
Urine sodium concentration	88 mmol/l

Urine potassium levels 49 mmol/l  
Urine calcium:creatinine ratio 0.3 (high)

Venous blood gas result

pH 7.532  
Bicarbonate 37 mmol/l

Which of the following diagnosis would be consistent with the above clinical picture?

[Liddle's syndrome10%](#)[Conn's syndrome7%](#)[Familial idiopathic hypercalciuria14%](#)[Bartter's syndrome44%](#)[Gitelman's syndrome25%](#)

Patients with hypokalaemia, metabolic alkalosis and a normal - low blood pressure the following differentials should be considered - diuretic abuse, Bartter's syndrome, Gitelman's syndrome. Bartter's syndrome is an autosomal recessive disorder where there is a genetic defect involving the sodium-potassium-chloride transporters in the thick ascending limb of the glomerulus, resulting in an inability to reabsorb chloride and sodium in the loop of Henle, and subsequent distal sodium delivery results in distal tubular sodium and bicarbonate reabsorption with potassium and chloride loss. Serum renin and aldosterone levels are high despite a low or normal blood pressure. Treatment includes NSAIDs, potassium-sparing diuretics, and electrolyte replacement.

The biochemistry profile of Bartter's syndrome is often indistinguishable from diuretic abuse, and this patient should have a urine diuretic screen.

Gitelman's syndrome is an autosomal recessive disorder with a genetic defect in the sodium-chloride transporter in the distal tubule and can present with a similar hypokalaemic, alkalotic profile to Bartter's syndrome. However they are often clinically asymptomatic or have milder symptoms, and they have hypocalciuria and hypomagnesaemia.

Liddle's syndrome is an autosomal dominant disorder which tends to present with hypertension, hypokalaemia and metabolic alkalosis. Conn's syndrome or hyperaldosteronism presents with hypertension and hypokalaemia. Patients with familial idiopathic hypercalciuria tend to be asymptomatic.

### **Bartter's syndrome**

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the  $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$  cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine



causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

#### Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

#### Question 4 of 108

A 53-year-old obese HGV driver, normally taking BD Novomix 30 insulin presents to your outpatient clinic to clarify some driving regulations he had overheard while eating with colleagues. He is extremely tearful and anxious. He is worried about losing his livelihood as a result of his diabetes.

He was first diagnosed with type 2 diabetes 9 years ago and became insulin dependent 2 years ago. He reports good compliance with insulin every day. However, 18 months ago, he took the same units of insulin after exercising and felt giddy. A spot blood glucose check demonstrated 2.8 mmol/l, which improved immediately after drinking Lucozade that he carried with him. No hospitalisation was required. He has no other past medical history. He has no visual field or peripheral nerve impairments. What is the advice you give him regarding driving?

[Can continue driving, review in 1 year38%](#)[Can continue driving, no further reviews required9%](#)[Must stop driving and give up license permanently5%](#)[Must stop driving temporarily and review in 6 months14%](#)[Patient can drive type 1 vehicles \(cars, motorcycles\) but not type 2 vehicles \(lorries, HGV\) and should reconsider his profession34%](#)

The salient points in this case history are that the patient, although insulin dependent for treating his type 2 diabetes, retains hypoglycaemia awareness. A recent change in the DVLA guidelines of May 2012 allows HGV drivers to retain their license even if taking insulin, provided they have not suffered from hypoglycaemia requiring the assistance of others within the past 12 months, and the patient has no visual field impairments. The patient must then be reviewed annually by a diabetes consultant, with 3 months of blood glucose monitoring data available. A 1-year license is then issued annually.

## **DVLA: diabetes mellitus**

Until recently people with diabetes who used insulin could not hold a HGV licence. The DVLA changed the rules in October 2011. The following standards need to be met (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):

- there has not been any severe hypoglycaemic event in the previous 12 months
- the driver has full hypoglycaemic awareness
- the driver must show adequate control of the condition by regular blood glucose monitoring\*, at least twice daily and at times relevant to driving
- the driver must demonstrate an understanding of the risks of hypoglycaemia
- there are no other debarring complications of diabetes

From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) licence need to complete a VDIAB11 form.

Other specific points for group 1 drivers:

- if on insulin then patient can drive a car as long as they have hypoglycaemic awareness, not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months and no relevant visual impairment. Drivers are normally contacted by DVLA
- if on tablets or exenatide no need to notify DVLA. If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- if diet controlled alone then no requirement to inform DVLA

\*to demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that applicants will need to have used blood glucose meters with a memory function to measure and record blood glucose levels for at least 3 months prior to submitting their application

Question 1 of 103

A 19 year-old man is referred by his GP to the outpatient department after having several episodes of collapse at college. He reports that during these episodes he feels tired and 'blacks out'. Afterwards, he feels shaky and weak. There is no tongue biting or incontinence during these

episodes and the patient reports that he often feels dizzy after standing up too quickly from a chair. The only other symptoms he reports is a sore throat that has persisted for a few weeks and lethargy.

On examination of the patient's mouth and throat, there are some white plaques located at the back of the tongue and throat. His sitting blood pressure is 130/80 mmHg and his standing blood pressure is 95/70 mmHg. He is otherwise well.

Blood tests are performed and reveal:

Hb	13.9 g/dL
Platelets	$200 \times 10^9/l$
WBC	$6.2 \times 10^9/l$
Na <sup>+</sup>	132 mmol/l
K <sup>+</sup>	5.1 mmol/l
Urea	4.7 mmol/l
Creatinine	81 $\mu$ mol/l
Calcium	1.9 mmol/l
Random glucose	3.9 mmol/l

What is the most likely diagnosis?

[Type II polyglandular autoimmune syndrome30% Thymoma4% Type 1 polyglandular autoimmune syndrome50% Type III polyglandular autoimmune syndrome8% HIV9%](#)

The most likely diagnosis is type 1 polyglandular autoimmune syndrome. This autosomal recessive syndrome is a subtype of autoimmune polyendocrine syndrome, whereby a number of endocrine glands dysfunction. The patient's oral candidiasis is caused by a mild immune deficiency and hyposplenism. Furthermore, the patient has hypocalcaemia, caused by autoimmune dysfunction of the parathyroid gland and hypoglycaemia with hypotension, caused by autoimmune dysfunction of the adrenal gland.

### **Autoimmune polyendocrinopathy syndrome**

Addison's disease (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients. There are two distinct types of autoimmune polyendocrinopathy syndrome (APS), with type 2 (sometimes referred to as Schmidt's syndrome) being much more common.

APS type 2 has a polygenic inheritance and is linked to HLA DR3/DR4. Patients have Addison's disease plus either:

- type 1 diabetes mellitus
- autoimmune thyroid disease

APS type 1 is occasionally referred to as Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC). It is a very rare autosomal recessive disorder caused by mutation of AIRE1 gene on chromosome 21

Features of APS type 1 (2 out of 3 needed)

- chronic mucocutaneous candidiasis (typically first feature as young child)
- Addison's disease
- primary hypoparathyroidism

Vitiligo can occur in both types

Question 2 of 103

A 55 year-old male presents to endocrine outpatient clinic for investigation of gynaecomastia. On examination he has bilateral growth of breast tissue with palpable glandular tissue around the areolae. His past medical history includes hypertension, hypothyroidism, and congestive cardiac failure. He drinks 30 units of alcohol per week. His regular medications include: levothyroxine, amlodipine, bisoprolol, lisinopril and spironolactone.

On examination he is of normal stature, there are no peripheral stigmata of chronic liver disease or testicular masses.

What is the most likely explanation of his gynaecomastia?

[Cirrhosis6% Hypopituitarism5% Iatrogenic78% Klinefelter's syndrome4% Idiopathic6%](#)

The most likely explanation for this gentleman's gynaecomastia given the negative examination findings is a side effect of his current regular medications. There are many drugs that can cause gynaecomastia; in this case the culprit could be either amlodipine or spironolactone.

## Gynaecomastia

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

### Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

### Drug causes of gynaecomastia

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- gonadorelin analogues e.g. Goserelin, buserelin
- oestrogens, anabolic steroids

### Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyl dopa

A 67-year-old type 2 diabetic visits you in endocrinology outpatients complaining of reduced mobility over the past 6 months. For the past 7 months, her blood glucose has been well controlled on the same regime of metformin and pioglitazone. In addition, she has a past medical history of two previous CABGs for ischaemic heart disease, hypertension and an active 35 pack year smoking history. She reports no orthopnoea or recent chest pain. On examination, her respiratory, cardiovascular and abdominal examinations are unremarkable. However, you note bilateral lower limb swelling to both knees, which she reports to have been of gradual onset over the past 6 months. You note no evidence of varicose veins or clinical signs of deep vein thrombosis. Urine dip is negative for glucose, leucocytes, nitrites and protein. A 12 lead ECG demonstrates normal sinus rhythm at 65/ minutes with normal voltage criteria. A recent echocardiogram 4 months ago demonstrates an ejection fraction of 60% with no regional wall abnormalities. What is the most likely diagnosis?

[Silent myocardial infarctions3% Undiagnosed congestive cardiac failure resulting in fluid overload6% Diabetic nephropathy resulting in nephrotic syndrome4% Chronic venous insufficiency6% Pioglitazone resulting in fluid retention81%](#)

Fluid retention is a common side effect of pioglitazone and hence should be avoided in patients with a known congestive cardiac failure. In this case, there is no evidence for a cardiac failure in the context of a relatively normal echocardiogram. In addition, it appears the fluid retention began 2 months prior to the normal echo. The additional lack of ECG changes suggest against cardiac ischaemia despite the number of risk factors. Diabetic nephropathy is a possibility but a nephrotic syndrome results in a protein losing nephropathy. It would be unusual for no protein to be detected on urine dip.

## **Thiazolidinediones**

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

### **Adverse effects**

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures

- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

#### Question 4 of 103

A 28-year-old pregnant lady presents to the Emergency Department with palpitations and sweating. She mentions that she has had these symptoms on and off for the past 4 months but that they have worsened over the past few weeks. Now she is feeling worried and wanted to be assessed medically due to her concern she was having a miscarriage. She looks particularly anxious to be in hospital. This is her first pregnancy. She is 7 weeks pregnant. She has had no vaginal bleeding or discharge during the course of her pregnancy. She is normally fit and well.

Initial observations reveal a blood pressure of 130/85 mmHg, a heart rate of 110 beats per minute, a respiratory rate of 19/min, oxygen saturations of 99% on air and a temperature of 37.5°C. Examination findings reveal a resting tachycardia and a subtle goitre is noted.

Blood test results are as follows:

Hb	110 g/l
Wcc	12 x10 <sup>9</sup> /l
Plt	245 x10 <sup>9</sup> /l
CRP	12 mg/l
Na+	140 mmol/l
K+	5.0 mmol/l
Ur	5.7 mmol/l
Cr	110 µmol/l
D-dimer	490 ng/ml
T4	21 mU/l
TSH	<0.05 pmol/l

Given the most likely diagnosis, how should this lady be managed?

[Watch and wait/symptomatic control with beta blockade18%](#)  
[Radioactive iodine therapy3%](#)  
[Subtotal thyroidectomy4%](#)  
[Propylthiouracil66%](#)  
[Block and replace carbimazole + thyroxine8%](#)

This lady has symptoms and biochemical evidence of hyperthyroidism. This lady's symptoms predate her pregnancy, therefore it is not pregnancy induced thyrotoxicosis and will not self-limit - she will need treatment to prevent complications to her and the foetus. Radioactive iodine is contraindicated. Subtotal thyroidectomy is a little risky and extreme during pregnancy.

Carbimazole, whilst normally first line, has been associated with neonatal aplasia cutis before 12 weeks gestation and is therefore usually avoided. This leaves propylthiouracil as the current safest option. During the second trimester, propylthiouracil should be changed to carbimazole due to the potential risk of hepatotoxicity with propylthiouracil. The lowest dose that controls the hyperthyroid state should be used as both medications can cross the placenta.

## **Pregnancy: thyroid problems**

In pregnancy there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level

### **Thyrotoxicosis**

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in second and third trimester

### **Management**

- propylthiouracil has traditionally been the antithyroid drug of choice. This approach was supported by the 2007 Endocrine Society consensus guidelines
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

### **Hypothyroidism**

#### **Key points**

- thyroxine is safe during pregnancy
- serum thyroid stimulating hormone measured in each trimester and 6-8 weeks post-partum
- some women require an increased dose of thyroxine during pregnancy
- breast feeding is safe whilst on thyroxine



### Question 5 of 103

A 72-year-old male was admitted drowsy and confused. His family describe a 4-day history of shortness of breath and a productive cough. His past medical history includes type 2 diabetes mellitus, hypertension and hypercholesterolaemia. He usually takes metformin 500 mg three times daily, gliclazide 80 mg twice daily, amlodipine 5 mg daily and simvastatin 40 mg nightly. On examination he is confused with dry mucous membranes, blood pressure of 100/50 mmHg, a pulse of 110/min, a temperature of 37.6 °C and a respiratory rate of 20/min. Course crepitations were found at the right base and his pulse was thready with a capillary refill of 3 seconds; jugular venous pressure was not visible. Capillary blood glucose was found to be HI.

A venous blood sample is taken:

Hb	129 g/l	Na <sup>+</sup>	161 mmol/l
Platelets	204 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.9 mmol/l
WBC	13.1 * 10 <sup>9</sup> /l	Urea	15.2 mmol/l
Neuts	11.9 * 10 <sup>9</sup> /l	Creatinine	97 µmol/l
Glucose	56 mmol/l	eGFR	62 mg/l
Ketones	1.9 mmol/l	HbA1c	75 mmol/mol
pH	7.35	HCO <sub>3</sub>	20 mmol/mol

What treatment would you initiate first?

[0.9% normal saline](#)[75%0.45 % normal saline](#)[12% Hartmann's solution](#)[5% Intravenous insulin](#)[4%5% dextrose](#)[5%](#)

The underlying diagnosis is hyperosmolar hyperglycaemic state (HHS) precipitated by a lower respiratory tract infection. The diagnosis is made when a patient shows marked hyperglycaemia and hypovolaemia with a serum osmolality > 320 mosm/kg in the absence of marked ketonaemia or acidosis. This patient is clinically dry with a glucose of 56 and a calculated osmolality of  $2(161+4.9) + 56 + 15 = 403$  mosm/kg with mild ketonaemia.

Despite this gentleman's hypernatraemia, the first line fluid therapy is 0.9% normal saline as patients in HHS are sodium deplete. One litre should be administered rapidly and electrolytes then repeated to gauge potassium requirements in further fluid bags. A small initial rise in sodium is expected and this should not discourage further use of normal saline. Insulin is not routinely started immediately in the absence of significant ketonaemia as glucose will fall with fluid therapy alone. When glucose stops falling insulin may be started if glucose still remains high. Too rapid correction of osmolality i.e. with aggressive insulin and fluids in combination can precipitate cerebral oedema.

Guidelines for the management of HHS can be found below:

<http://www.diabetologists-abcd.org.uk/JBDS/JBDSIPHHSAdults.pdf>

## Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality  $>320 \text{ mosmol/kg}$
- Hyperglycaemia  $>30 \text{ mmol/L}$  with  $\text{pH} >7.3$ , bicarbonate  $>15 \text{ mmol/L}$  and no significant ketonuria  $<3 \text{ mmol/L}$

Question 8 of 103

A 70-year-old man with a history of smoking 15 cigarettes/day presents with drowsiness, weight loss and a persistent cough. His investigations show:

$\text{Na}^+$	115 mmol/L	135-145 mmol/L
$\text{K}^+$	5.1 mmol/L	3.5 - 5.0 mmol/L
Urea	3 mmol/L	2.0-7 mmol/L
Creatinine	74 $\mu\text{mol/L}$	55-120 $\mu\text{mol/L}$

Plasma osmolality 270 mOsm/kg 285-295 mOsm/kg

Urine osmolality 1210 500 - 800 mOsm/kg

What is the most likely diagnosis?

[Small cell lung cancer80%](#)[Hypothyroidism4%](#)[Encephalitis4%](#)[Congestive cardiac failure4%](#)[Squamous cell carcinoma9%](#)

Hyponatraemia, reduced plasma osmolality and increased urine osmolality are suggestive of syndrome of inappropriate ADH secretion (SIADH).

The increase in ADH causes more aquaporin utilisation in the collecting duct system of the kidney. This causes more water to be retained, diluting the electrolytes in the blood and making the electrolytes in the urine more concentrated.

Small cell lung cancer is a common cause of SIADH and is the most likely diagnosis in this man with an extensive smoking history, cough and weight loss.

## SIADH: causes

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

### Causes of SIADH

Category	Examples
Malignancy	<ul style="list-style-type: none"><li>• <b>small cell lung cancer</b></li><li>• also: pancreas, prostate</li></ul>
Neurological	<ul style="list-style-type: none"><li>• stroke</li><li>• subarachnoid haemorrhage</li><li>• subdural haemorrhage</li><li>• meningitis/encephalitis/abscess</li></ul>
Infections	<ul style="list-style-type: none"><li>• tuberculosis</li><li>• pneumonia</li></ul>
Drugs	<ul style="list-style-type: none"><li>• sulfonylureas*</li><li>• SSRIs, tricyclics</li><li>• carbamazepine</li><li>• vincristine</li><li>• cyclophosphamide</li></ul>
Other causes	<ul style="list-style-type: none"><li>• positive end-expiratory pressure (PEEP)</li><li>• porphyrias</li></ul>

### Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

\*the BNF states this has been reported with glimepiride and glipizide.

### Question 10 of 103

A surgical Foundation Year 1 doctor (FY1) asks you to review a preoperative ECG for a 19-year-old patient who has been admitted under their team with suspected appendicitis. The only abnormality is a prolonged QT and you note the adjusted calcium to be 2.02 mmol/l.

The FY1 tells you that when they looked at the patient's closed fists the outer two knuckles looked like dimples. She also tells you that the patient's body mass index is 29 kg/m<sup>2</sup>.

You ask her to order some blood tests which come back as follows:

Adjusted calcium 2.02 mmol/l

PTH 69 pmol/L (normal range = 0.8 - 8.5)

Phosphate 2.0 mmol/l

ALP 130 u/l

What is the most likely underlying cause for this patient's hypocalcaemia?

[Hypoparathyroidism5%](#)[Pseudohypoparathyroidism type 1a44%](#)[Pseudohypoparathyroidism type 1b13%](#)[Pseudopseudohypoparathyroidism17%](#)[Secondary hyperparathyroidism20%](#)

This patient has a high PTH, a low calcium, a high phosphate and a normal ALP. The patient is also obese and the dimples on the outer two knuckles are likely to represent shortening of the 4th and 5th metacarpals. This biochemistry in combination of these clinical features is characteristic of pseudohypoparathyroidism Type 1a (Albright's Hereditary Osteodystrophy).

Pseudopseudohypoparathyroidism would have the same clinical features but would have normal biochemistry. Pseudohypoparathyroidism Type 1b would have the same biochemistry but lack the clinical features.

This patient has a high PTH, therefore this immediately excludes hypoparathyroidism. In secondary hyperparathyroidism the ALP would be elevated therefore this is incorrect.

### **Pseudohypoparathyroidism**

Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in a G-protein. In type I pseudohypoparathyroidism there is a complete receptor defect whereas in type II the cell receptor is intact. Pseudohypoparathyroidism is typically inherited in an autosomal dominant fashion\*

## Bloods

- PTH: high
- calcium: low
- phosphate: high

## Features

- short fourth and fifth metacarpals
- short stature
- cognitive impairment
- obesity
- round face

## Investigation

- infusion of PTH followed by measurement of urinary phosphate and cAMP measurement  
- this can help differentiate between type I (neither phosphate or cAMP levels rise) and II (cAMP rises but phosphate levels do not change)

\*it was previously thought to be an X-linked dominant condition

## Question 1 of 93

A 52-year-old male presented with poor concentration, weight gain and tiredness for nine months duration. Three years ago he underwent resection of a pituitary tumour and was commenced on hydrocortisone 10 mg twice per day and thyroxine 150 g daily.

Examination reveals nothing significant.

Investigations show:

Serum free T4	12 pmol/L
Serum TSH	< 0.05 mU/L
Serum testosterone	7.3 nmol/L (10-30)
IGF-1	8.9 nmol/L (10-35)

What is the most appropriate treatment for this patient?

Reduce the dose of thyroxine 13% Reduce the dose of hydrocortisone 16% Increase the dose of hydrocortisone 21% Testosterone injection 16% Growth hormone 35%

This man with panhypopituitarism is receiving adequate replacement of hydrocortisone and thyroxine.

In panhypopituitarism the TSH is low so the thyroxine replacement is monitored by the free T4 which is within the normal range in this case.

Symptoms of weight gain, tiredness and poor concentration are typical of growth hormone deficiency which is further supported by the low IGF-1.

Indeed, this gentleman is also requiring testosterone replacement but this is not the best answer here.

## **Pituitary tumours**

Hormones secreted

- prolactin- 35%
- no obvious hormone, 'non-functioning', 'chromophobe' - 30%
- growth hormone - 20%
- prolactin and growth hormone - 7%
- ACTH - 7%
- others: TSH, LH, FSH - 1%

Question 2 of 93

A middle age woman is being treated for symptomatic hypercalcaemia associated with a squamous cell lung cancer (serum calcium 3.60 mmol/L). She is slow to respond to initial measures of saline hydration and intravenous pamidronate. Whilst awaiting surgical resection for her underlying cancer what may be the next best step in her management?

Na <sup>+</sup>	142 mmol/l
K <sup>+</sup>	4.3 mmol/l
Urea	7.0 mmol/l

Creatinine 89  $\mu\text{mol/l}$

Glucose 4.8  $\text{mmol/l}$

What is the most appropriate management?

[High dose loop diuretics 26% Calcitonin 4 units/kg 62% Insulin actrapid 50 units in 50% dextrose 5% IV colloid administration instead of crystalloid 3% Plasma exchange 3%](#)

General symptoms of hypercalcaemia may include malaise, lethargy, depression, dehydration and can lead to depressed consciousness. Bone pain and abdominal pain may feature and can be summarised by the classic 'bones, stones, moans and abdominal groans'.

Alongside searching for the underlying cause, management initially involves aggressive rehydration, typically 4-6 L saline on the first day. Bisphosphonates act by interfering with osteoclastic bone resorption and typically IV pamidronate is used at a dose of 60-90mg over 2-4 hours. Calcitonin (extracted from salmon) also interferes with osteoclast activity as well as increasing renal calcium excretion.

Diuretics may lead to further dehydration. Dialysis may be a last line treatment for life threatening hypercalcaemia, but not plasma exchange.

### **Hypercalcaemia: management**

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

Loop diuretics such as furosemide are sometimes used in hypercalcaemia, particularly in patients who cannot tolerate aggressive fluid rehydration. However, they should be used with caution as they may worsen electrolyte derangement and volume depletion.

### Question 3 of 93

A 42-year-old lady comes to see you in outpatients. Incidentally, you notice that her TSH was  $< 0.1$  mU/l on a recent blood test requested by the GP. Her only past medical history is thyroid cancer which has been resected and her only medication levothyroxine 100mcg per day.

She is otherwise asymptomatic. What is the best course of action?

[Stop levothyroxine5%](#)[Continue at 100mcg per day37%](#)[Repeat thyroid function in 6 weeks21%](#)[Change to liothyronine equivalent dose5%](#)[Reduce the levothyroxine as she is over treated32%](#)

As TSH is a growth factor for many thyroid cancers it is routinely suppressed with levothyroxine. TSH and thyroglobulin should be monitored in patients with a history of thyroid cancer and decisions on the level required are usually specialist led.

High and intermediate risk patients should have their TSH suppressed below 0.1 mU/l and low-risk patients TSH should be 0.1-0.5 mU/l.

As she is asymptomatic and her TSH is adequately suppressed this lady should be maintained on her current dose pending specialist review.

British Thyroid Association, guidelines for the management of thyroid cancer (2014) and The American Thyroid Associations Guidelines (2009).

## Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

### Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Management of papillary and follicular cancer



- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

### Further information

Type	Notes
Papillary carcinoma	<ul style="list-style-type: none"> <li>• Usually contain a mixture of papillary and colloidal filled follicles</li> <li>• Histologically tumour has papillary projections and pale empty nuclei</li> <li>• Seldom encapsulated</li> <li>• Lymph node metastasis predominate</li> <li>• Haematogenous metastasis rare</li> </ul>
Follicular adenoma	<ul style="list-style-type: none"> <li>• Usually present as a solitary thyroid nodule</li> <li>• Malignancy can only be excluded on formal histological assessment</li> </ul>
Follicular carcinoma	<ul style="list-style-type: none"> <li>• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.</li> <li>• Vascular invasion predominates</li> <li>• Multifocal disease rare</li> </ul>
Medullary carcinoma	<ul style="list-style-type: none"> <li>• C cells derived from neural crest and not thyroid tissue</li> <li>• Serum calcitonin levels often raised</li> <li>• Familial genetic disease accounts for up to 20% cases</li> <li>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.</li> </ul>
Anaplastic carcinoma	<ul style="list-style-type: none"> <li>• Most common in elderly females</li> <li>• Local invasion is a common feature</li> <li>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.</li> </ul>

### Question 4 of 93

A 50-year-old gentleman presents to review in the endocrine clinic. He was normally taking metformin and gliclazide, but over the last six months has also been prescribed a GLP-1 mimetic. He was started on a GLP-1 mimetic because of poor diabetic control and concerns about starting insulin. He does not want to start insulin because he is a truck driver and worried about losing his driving license. He had previously tried the combination of metformin, gliclazide and pioglitazone, but this had also failed to control his HbA1c.

Over the last six months his HbA1c has reduced from 81mmol/ mol to 80mmol/ mol, and he has lost two kg in weight. What is the most appropriate action?

[Continue current treatment and review in one year5%](#)[Continue current treatment and review in six months31%](#)[Change to metformin, gliclazide and pioglitazone6%](#)[Offer to add on insulin13%](#)[Stop GLP-1 mimetic and offer insulin treatment45%](#)

The correct answer is to stop GLP-1 mimetic and offer insulin treatment. This is a patient with diabetes whose diabetic control has not improved even when on a combination of metformin and two other drugs. He was then started on GLP-1 mimetic therapy, but nice advice that this should only be continued if after six months HbA1c reduces by at least 11 mmol/mol, which has not happened. Therefore continuing the current treatment is incorrect. Insulin should not be combined with a GLP-1 mimetic.

Source:

'Type 2 diabetes in adults: management.' NICE guideline [NG28]. The National Institute for Health and Care Excellence, December 2015.

## **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids

- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

## HbA1c targets

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

Practical examples

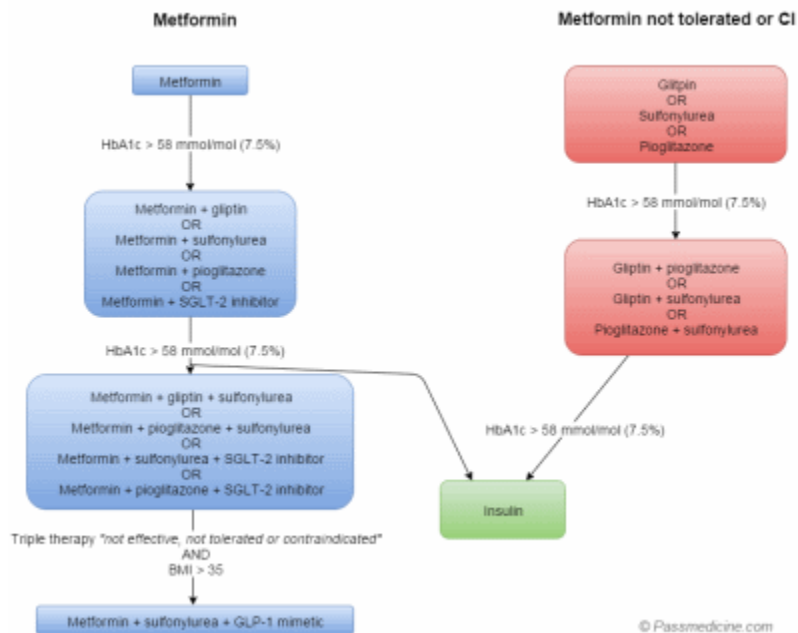
- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

## Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



### Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  - sulfonylurea
  - gliptin
  - pioglitazone
  - SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  - metformin + gliptin + sulfonylurea
  - metformin + pioglitazone + sulfonylurea
  - metformin + sulfonylurea + SGLT-2 inhibitor
  - metformin + pioglitazone + SGLT-2 inhibitor
  - OR insulin therapy should be considered

Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
- → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or
- → BMI  $< 35$  kg/m<sup>2</sup> and for whom insulin therapy would have significant occupational implications or

weight loss would benefit other significant obesityrelated comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

### Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

### Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

### Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: *'Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

## Risk factor modification

### Blood pressure

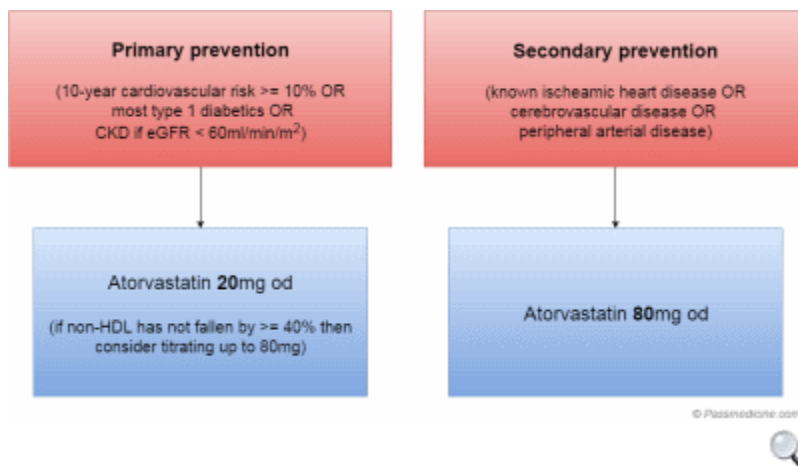
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

### Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



Graphic showing choice of statin.

\*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

### Question 5 of 93

A 45-year-old gentleman presents to clinic for review. Two weeks ago he presented to the emergency department with renal colic. A spiral CT KUB confirmed nephrolithiasis and he was managed conservatively with IV fluids, analgesia and an alpha-blocker. His symptoms resolved entirely and he was discharged.

Blood tests:

Hb	142 g/l
Platelets	$329 \times 10^9/l$
WBC	$6.6 \times 10^9/l$
Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	3.8 mmol/l
Urea	6.2 mmol/l
Creatinine	71 $\mu$ mol/l
Corrected calcium	2.71 mmol/l
Parathyroid hormone	10.2 pmol/l

Urine tests (24-hour collection):

Urinary calcium 183 mg

How should he be further managed?

[Annual monitoring of calcium and renal function11%Encourage oral fluids18%Bisphosphonates14%Vitamin D supplementation7%Parathyroidectomy50%](#)

The correct answer is parathyroidectomy. This is a patient who has developed renal colic secondary to likely primary hyperparathyroidism, as is suggested by his hypercalcaemia and elevated parathyroid hormone. The mainstay of management of primary hyperparathyroidism is parathyroidectomy, but cases have to be appropriately identified as surgical candidates. This patient developed renal stones as a likely complication and therefore would benefit from surgery. If the blood tests been an incidental finding, then monitoring and oral fluids both would have been more appropriate.

Source:

'Hypercalcaemia.' Clinical Knowledge Summaries. National Institute for Health and Care Excellence, Dec. 2014.

## **Primary hyperparathyroidism**

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Features - 'bones, stones, abdominal groans and psychic moans'

- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture
- renal stones
- depression
- hypertension

Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- raised calcium, low phosphate



- PTH may be raised or normal
- technetium-MIBI subtraction scan

#### Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- calcimimetic agents such as cinacalcet are sometimes used in patients who are unsuitable for surgery





Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

#### Question 6 of 93

A 58 year-old man presents with a two month history of weight loss and a one week history of increasing confusion. His partner reports that his clothes are now loose on him and that he has started to forget things and that he has been unable to reach for objects off the top shelf at the supermarket over the last two months due to increasing weakness. Six weeks ago he had been treated for an islet cell carcinoma of the pancreas with chemotherapy and has no other past medical history.

Examination reveals an abbreviated mental test score of 5/10 and weakness in the shoulders and getting out of the chair. Heart sounds 1 and 2 are present with no added sounds, his chest is clear and the abdomen is soft and non-tender.

Observations reveal a blood pressure of 158/95 mmHg, a pulse rate of 90 beats per minute, a temperature of 37.5°C and a respiratory rate of 14 breaths per minute. Random blood glucose is 16.2 mmol/L.

Blood tests are performed and reveal:

Hb	14.2 g/l
Platelets	$180 \times 10^9/l$
WBC	$4.9 \times 10^9/l$
Na <sup>+</sup>	150 mmol/l
K <sup>+</sup>	2.6 mmol/l
Urea	5.2 mmol/l
Creatinine	100 µmol/l
Bilirubin	15 µmol/l
ALP	70 u/l
ALT	28 u/l
γGT	47 u/l
Albumin	48 g/l

What is the most likely diagnosis?

[Paraneoplastic encephalitis15% Cerebral metastases7% Post chemotherapy Cushing's syndrome30% Post chemotherapy hypothyroidism4% Ectopic ACTH secretion43%](#)

The confusion, hypertension and proximal myopathy, along with the hypernatraemia, hypokalaemia and hyperglycaemia all point towards a diagnosis of Cushing's syndrome. The subtype is most likely ectopic secretion of ACTH by the islet cell carcinoma, a neuroendocrine tumour and can release ectopic hormones. The post-chemotherapy Cushing's syndrome is unlikely, as the chemotherapy started after the proximal myopathy had begun to take effect. Further, in ectopic ACTH secretion, the hypokalaemia tends to be more pronounced, as in this case.

### **Cushing's syndrome: causes**

#### ACTH dependent causes

- Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
- ectopic ACTH production (5-10%): e.g. small cell lung cancer

#### ACTH independent causes

- iatrogenic: steroids
- adrenal adenoma (5-10%)
- adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma
- micronodular adrenal dysplasia (very rare)

#### Pseudo-Cushing's

- mimics Cushing's
- often due to alcohol excess or severe depression
- causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- insulin stress test may be used to differentiate

A 78-year-old man is investigated for headaches. A routine blood screen is normal other than an elevated ALP. A skull x-ray is ordered:



© Image used on license from [Radiopaedia](#)



What is the most likely diagnosis?

[Myeloma5%](#)[Cervical spondylosis4%](#)[Pituitary tumour4%](#)[Calcified temporal arteritis6%](#)[Paget's disease of the bone81%](#)

This is a very stereotypical question - you should always think Paget's disease if shown a skull x-ray in an exam.

The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.

**Paget's disease of the bone**

Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

#### Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium\* and phosphate are typically normal
- skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's

- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

#### Complications

- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



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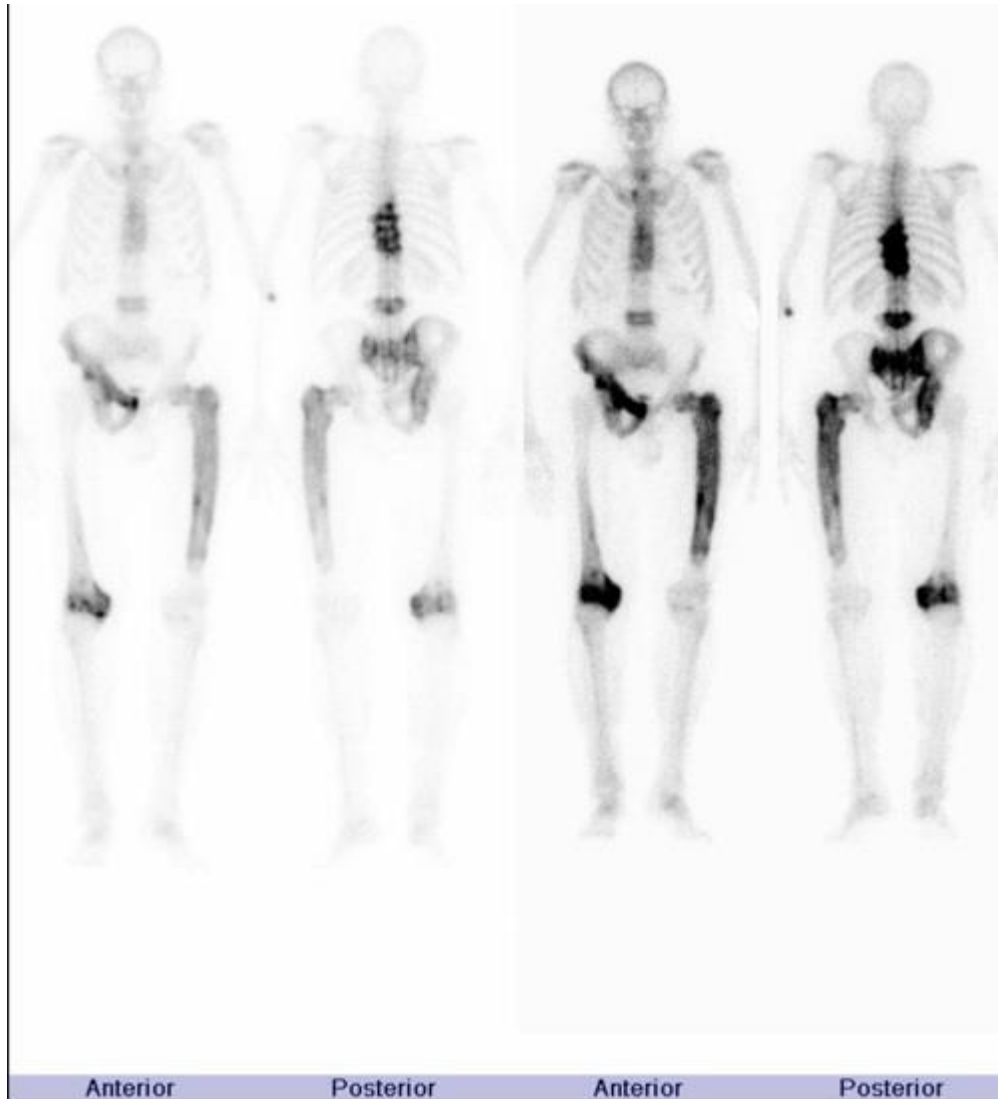


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Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.





© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilization

You are seeing a 50-year-old lady with type 2 diabetes mellitus in the outpatient clinic. She has a past medical history of gastritis, moderate left ventricular dysfunction and chronic obstructive pulmonary disease. She is currently on metformin and gliclazide. Since last review she has gained 5kg in weight and her HbA1c has deteriorated to 70 mmol/mol from 62 mmol/mol. Body mass index today in clinic is 33 kg/m<sup>2</sup>.

Recent blood tests are as follows:

Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	3.9 mmol/l
Urea	6 mmol/l
Creatinine	140 µmol/l

She was unable to previously tolerate liraglutide due to nausea and vomiting. What would be the best alteration to her therapy?

[Empagliflozin \(SGLT-2 inhibitor\)58%Add insulin18%Add pioglitazone10%Increase dose of metformin10%Increase dose of gliclazide5%](#)

SGLT inhibitors have the advantage of improving glycaemic control/HbA1c and having beneficial effects on weight. This is because their mode of action is independent of insulin release. They act upon the SGLT-2 receptors in the kidney and lead to increased loss of glucose in the urine.

## **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

## Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

## HbA1c targets

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

## Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

## Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

## Patient already on treatment

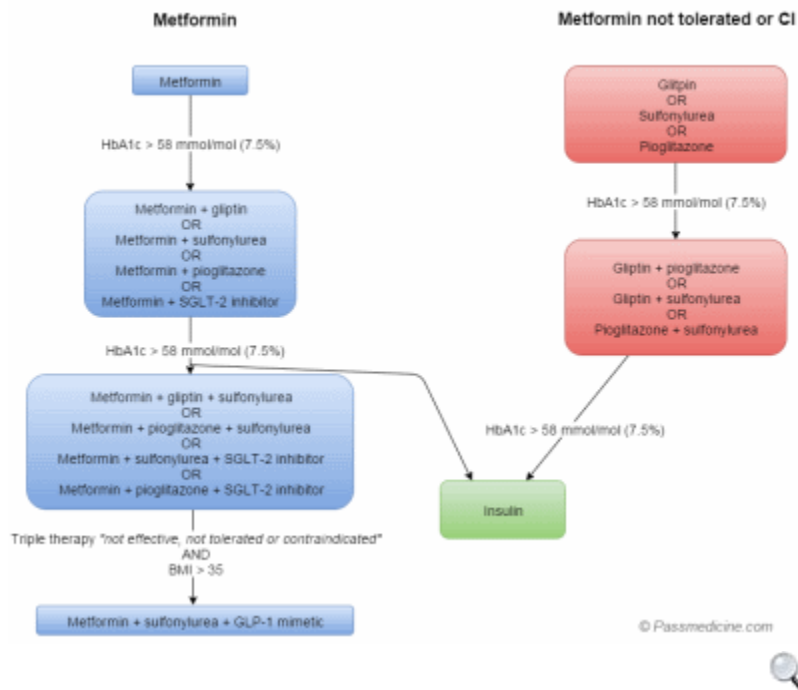
## Management of T2DM

## HbA1c target

Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%) 53 mmol/mol (7.0%)

### Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



### Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
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  - → gliptin
  - → pioglitazone
  - → SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  - → metformin + gliptin + sulfonylurea
  - → metformin + pioglitazone + sulfonylurea
  - → metformin + sulfonylurea + SGLT-2 inhibitor
  - → metformin + pioglitazone + SGLT-2 inhibitor

- → OR insulin therapy should be considered

#### Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
  - → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or
  - → BMI  $< 35$  kg/m<sup>2</sup> and for whom insulin therapy would have significant occupational implications or

weight loss would benefit other significant obesityrelated comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

#### Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

#### Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

#### Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: *'Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

## Risk factor modification

### Blood pressure

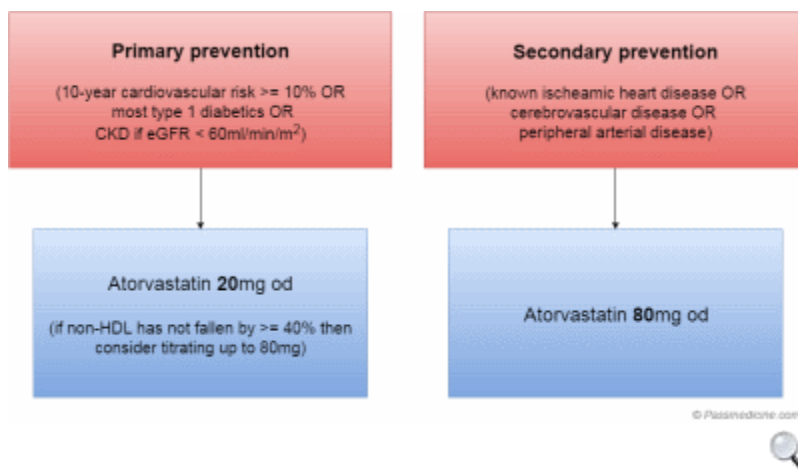
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

### Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



Graphic showing choice of statin.

\*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their

HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

#### Question 8 of 93

You are seeing a 50-year-old lady with type 2 diabetes mellitus in the outpatient clinic. She has a past medical history of gastritis, moderate left ventricular dysfunction and chronic obstructive pulmonary disease. She is currently on metformin and gliclazide. Since last review she has gained 5kg in weight and her HbA1c has deteriorated to 70 mmol/mol from 62 mmol/mol. Body mass index today in clinic is 33 kg/m<sup>2</sup>.

Recent blood tests are as follows:

Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	3.9 mmol/l
Urea	6 mmol/l
Creatinine	140 µmol/l

She was unable to previously tolerate liraglutide due to nausea and vomiting. What would be the best alteration to her therapy?

[Empagliflozin \(SGLT-2 inhibitor\)58%](#)[Add insulin18%](#)[Add pioglitazone10%](#)[Increase dose of metformin10%](#)[Increase dose of gliclazide5%](#)

SGLT inhibitors have the advantage of improving glycaemic control/HbA1c and having beneficial effects on weight. This is because their mode of action is independent of insulin release. They act upon the SGLT-2 receptors in the kidney and lead to increased loss of glucose in the urine.

### **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

#### Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

#### HbA1c targets

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

#### Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

#### Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors



Patient already on treatment

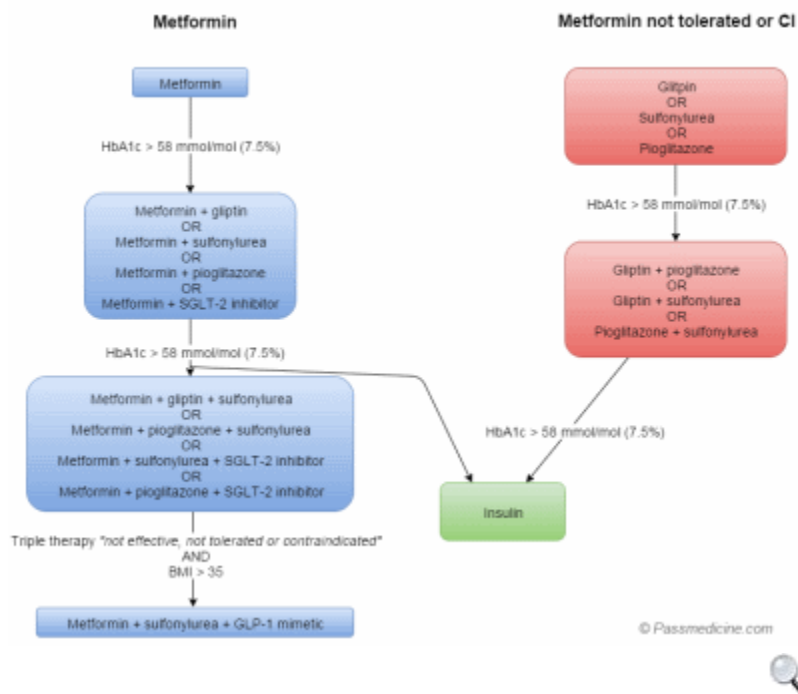
## Management of T2DM

## HbA1c target

Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%) 53 mmol/mol (7.0%)

## Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



## Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
  - → SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
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- → metformin + pioglitazone + sulfonylurea
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- → metformin + pioglitazone + SGLT-2 inhibitor
- → OR insulin therapy should be considered

Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
  - → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or
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weight loss would benefit other significant obesityrelated comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
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## Risk factor modification

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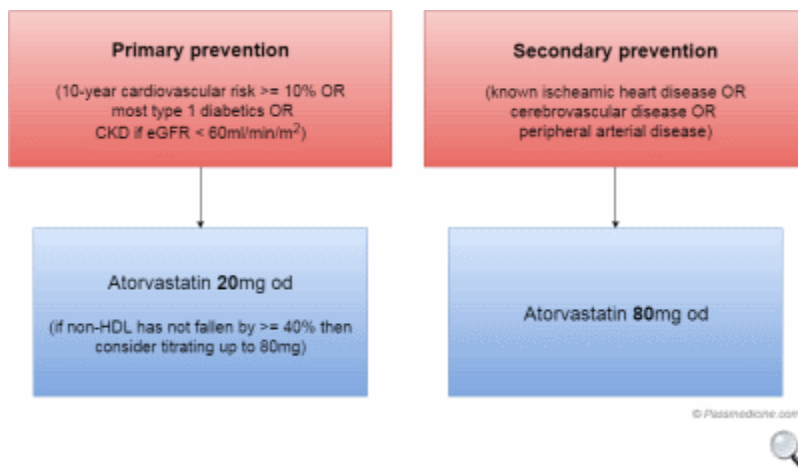
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### Antiplatelets

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### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



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(6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

#### Question 9 of 93

A 32 year-old man is referred by his GP after collapsing while at work. He does not remember the episode but witnesses say that there was no incontinence or fitting and the patient does not have a sore mouth or tongue. This is the first time this has happened and the patient does not have any other past medical history of note and takes no regular medication.

Examination reveals a blood pressure of 162/95 mmHg, a pulse of 74 beats per minute, a respiratory rate of 16 and a temperature of 37.4°C. Heart sounds 1 and 2 are present with no added sounds, the lung fields are clear and his abdomen is soft and non-tender.

Blood tests performed and reveal:

Na <sup>+</sup>	143 mmol/l
K <sup>+</sup>	3.0 mmol/l
Urea	5.6 mmol/l
Creatinine	76 µmol/l
Bicarbonate	31 mmol/l
Renin	low
Aldosterone	low

Which of the following is the best treatment?

[Amiloride59%](#) [Bumetanide6%](#) [Spironolactone21%](#) [ACE inhibitor9%](#) [Angiotensin II receptor blocker6%](#)

This man has Liddle's syndrome, an autosomal dominant disorder characterised by hypertension associated with hypokalaemic metabolic alkalosis, low plasma renin activity, and suppressed aldosterone secretion. Amiloride is the best treatment for the hypertension and hypokalaemia as it acts on the sodium channels directly, as opposed to spironolactone, which acts on mineralocorticoid receptors.

#### **Liddle's syndrome**

Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

Treatment is with either amiloride or triamterene

Question 2 of 83

A 55-year-old man presents to the endocrine clinic. He was diagnosed five years ago with type 2 diabetes and is struggling to control his sugars. He is currently taking:

Metformin 1g BD  
Glicazide 160mg BD  
Sitagliptin 100mg OD

He is a bus driver and struggles to control his weight with his hectic shifts. Current BMI is 34 kg/m<sup>2</sup>.

Investigations:

Serum creatinine 120 µmol/L (60-110)  
Haemoglobin A1c 66 mmol/mol (8.2%)

What would be the most appropriate next step?

[Canagliflozin14%Glibenclamide 5%Increase metformin6%Stop sitagliptin and add insulin9%Stop sitagliptin and add exenatide66%](#)

Given the NICE guidance the most appropriate step would be to start this patient on exenatide. This patient is already on metformin, glicazide and sitagliptin and the blood sugar levels are not under control. His BMI is under 35 but insulin would make 'it much more difficult for you to do your job'.

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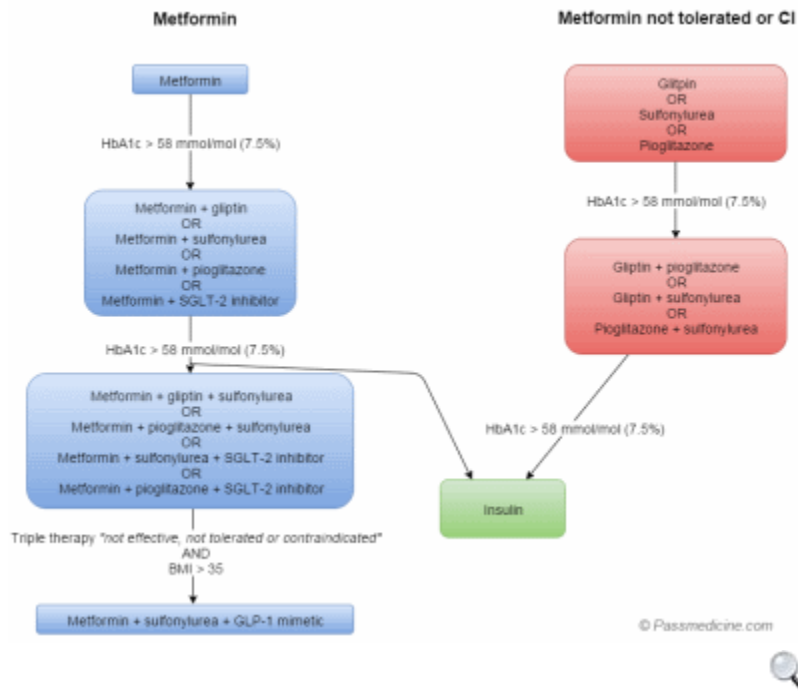
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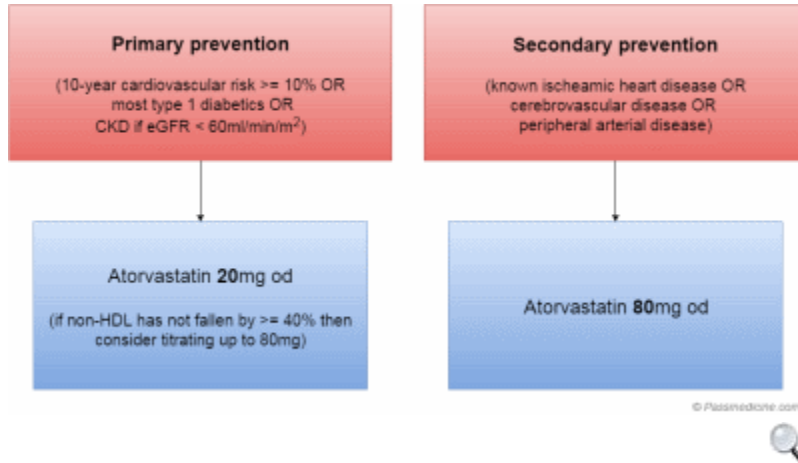
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Question 3 of 83

A 58-year-old patient who has a history of hypertension is operated on by the neurosurgeons for an intracranial haemorrhage.

Over the next few days his serum sodium level progressively declines and by the third day has fallen to 118 mmol/l despite fluid restriction to 1L per day. Urine osmolality is 700 mOsmol/l and urinary sodium is raised at 80 mmol/l.

What is the most likely diagnosis?

[Addisonian crisis 7%](#) [Secretion of inappropriate antidiuretic hormone 64%](#) [Cranial diabetes insipidus 22%](#) [Hypovolaemia 4%](#) [Fluid overload 3%](#)

The hyponatraemia and hypotonic blood plasma, coupled with the raised urine osmolality and raised urinary sodium excretion indicates a diagnosis of syndrome of inappropriate ADH secretion. This is a condition that can occur after head trauma, a central nervous system infection and intracranial haemorrhage.

**SIADH: causes**

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

### Causes of SIADH

Category	Examples
Malignancy	<ul style="list-style-type: none"><li>• <b>small cell lung cancer</b></li><li>• also: pancreas, prostate</li></ul>
Neurological	<ul style="list-style-type: none"><li>• stroke</li><li>• subarachnoid haemorrhage</li><li>• subdural haemorrhage</li><li>• meningitis/encephalitis/abscess</li></ul>
Infections	<ul style="list-style-type: none"><li>• tuberculosis</li><li>• pneumonia</li></ul>
Drugs	<ul style="list-style-type: none"><li>• sulfonylureas*</li><li>• SSRIs, tricyclics</li><li>• carbamazepine</li><li>• vincristine</li><li>• cyclophosphamide</li></ul>
Other causes	<ul style="list-style-type: none"><li>• positive end-expiratory pressure (PEEP)</li><li>• porphyrias</li></ul>

### Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

\*the BNF states this has been reported with glimepiride and glipizide.

### Question 4 of 83

You are asked to review a 62 year-old Caucasian man who is an inpatient on the medical admissions unit. He is currently being treated for a left lower lobe community acquired

pneumonia. You note consumed alcohol excessively prior to admission but has been abstinent for the last four days.

During this admission it has been noted that serial bloods glucose measurements have been elevated and subsequently a new diagnosis type two diabetes has been made. The admission consultant noted Cushingoid features and requested an overnight low dose dexamethasone suppression test. The results are as follows:

8am Cortisol after 1mg dexamethasone at 11pm the previous day	438 nmol/L
Reference range for serum cortisol	170-540 nmol/L

What is most appropriate next step in the investigation of this gentleman?

[Serum ACTH measurement24% Midnight serum cortisol25% Inferior petrosal sinus sampling post CRH administration8% High dose dexamethasone suppression test32% MRI pituitary10%](#)

Pseudo-Cushing's syndrome is common in those with excessive alcohol consumption. The physical signs resemble true Cushing's syndrome however the aetiology is idiopathic rather than dysfunction of the hypothalamic-pituitary axis. It is therefore important to exclude pseudo-Cushing's prior to further investigation.

The hallmark of true Cushing's syndrome is lack of diurnal variation in serum cortisol. However in pseudo-Cushing's diurnal variation is normally maintained. Those with pseudo-Cushing's will have elevated 24 hour urinary cortisol and will also fail to suppress serum cortisol with a low dose dexamethasone suppression test. The correct approach in this case is therefore to measure a midnight cortisol prior to proceeding to further investigation.

Papanicolaou DA, Yanovski JA, Cutler GB Jr. A single midnight serum cortisol measurement distinguishes Cushing's syndrome from pseudo-Cushing states. J Clin Endocrinol Metab. 1998 Apr. 83(4):1163-7.

### **Cushing's syndrome: investigations**

Investigations are divided into confirming Cushing's syndrome and then localising the lesion. A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance. Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels. An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's

## Tests to confirm Cushing's syndrome

The two most commonly used tests are:

- overnight dexamethasone suppression test (most sensitive)
- 24 hr urinary free cortisol

## Localisation tests

The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

High-dose dexamethasone suppression test

- if pituitary source then cortisol suppressed
- if ectopic/adrenal then no change in cortisol

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic ACTH secretion

## Question 5 of 83

A lady who is 10 weeks pregnant presents to her antenatal appointment asking for advice regarding gestational diabetes. She is a 31 year old English lady with a BMI (body mass index) of 28.7. In terms of family history she has a cousin who has type 1 diabetes mellitus and an aunt who is being treated for breast cancer. She has had two previous pregnancies, the first one she unfortunately miscarried at 8 weeks, and the second was a normal pregnancy that she took to term with a birth weight of 4.6kg. Neither of these pregnancies was complicated with gestational diabetes, and the baby is now 2 years old and has not had to be taken to see a doctor other than routine appointments.

What is the most appropriate testing regime for ruling out gestational diabetes in this woman?

[Oral glucose tolerance test at 24-28 weeks pregnant45%None - as she has no risk factors for gestational diabetes6%Oral glucose tolerance test at 12-14 weeks pregnant37%Self-monitoring of sugars and repeat appointment in 2 weeks8%HBa1c5%](#)

This question requires knowledge on the risk factors for developing gestational diabetes and appropriate testing based on risk:

Risk factors for gestational diabetes include:

- BMI  $>30\text{kg/m}^2$
- Previous delivery of a baby over 4.5kg - which qualifies this patient
- Previous gestational diabetes
- Family history of diabetes (1st degree relative)
- Minority ethnic family origin with a high prevalence of diabetes

If any one of these risk factors is present then one should offer testing for gestational diabetes. The gold standard testing for patients with risk factors is 2-hour 75g oral glucose tolerance test (OGTT) at 24-28 weeks gestation. If the patient has had gestational diabetes in a previous pregnancy then early-self monitoring of blood glucose or OGTT as soon as possible after booking could also be used for diagnosis.

A diagnosis of gestational diabetes is made if the patient has either:  
Fasting glucose of 5.6 mmol/L or above OR  
A 2-h plasma glucose of 7.8 mmol/L or above

<http://www.nice.org.uk/guidance/ng3/chapter/1-recommendations>

## **Pregnancy: diabetes mellitus**

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates around 1 in 40 pregnancies. NICE updated the guidance in 2015

Risk factors for gestational diabetes

- BMI of  $> 30\text{ kg/m}^2$
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- women who've previously had gestational diabetes: oral glucose tolerance test (OGTT) should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

#### Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is  $\geq 5.6$  mmol/l
- 2-hour glucose is  $\geq 7.8$  mmol/l

#### Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about selfmonitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is  $< 7$  mmol/l a trial of diet and exercise should be offered
- if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
- if glucose targets are still not met insulin should be added to diet/exercise/metformin
- if at the time of diagnosis the fasting glucose level is  $\geq 7$  mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

#### Management of pre-existing diabetes

- weight loss for women with BMI of  $> 27$  kg/m<sup>2</sup>
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

#### **Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)**

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

#### Question 6 of 83

A 27-year-old female presents with secondary amenorrhoea after stopping the oral contraceptive pill 6 months ago. She gets regular headaches and struggles to stand from seated or climb stairs.

On examination, milk could be expressed from the breasts and visual fields showed bilateral defects in the upper outer quadrants.

Prolactin	1080 mIU/L (NR<360)
FSH	0.1 IU/L (NR 1-11)
LH	0.2 IU/L (NR 20-75)
TSH	0.1 mIU/L (NR 0.3-6.0)
T4	8 pmol/L (NR 10-25)
9am cortisol	20 nmol/L (NR 140-700)

Pituitary MRI: 3cm pituitary mass with tenting of optic chiasm.

What is the next step in management?

[Bromocriptine34%](#)[Octreotide5%](#)[Stereotactic radiotherapy3%](#)[Trans-sphenoidal surgery54%](#)[Transcranial hypophysectomy4%](#)

This patient has a macroadenoma (>1cm) causing visual field defects. Trans-sphenoidal surgery is the first step in management. Raised prolactin can be secondary to blockage of the pituitary stalk with prevention of dopamine reaching the pituitary causing disinhibition of the lactotrophs.

Prolactin secreting macroadenomas secrete very high quantities and PRL is usually >6000mU/ml particularly with macro-prolactinomas (this is not the case making a prolactinoma unlikely). Prolactinomas are treated with dopamine agonists (bromocriptine, cabergoline) first-line. Octreotide is used to treat acromegaly.

Transcranial hypophysectomy is done for very large tumours that cant be removed via the trans-sphenoidal route.



## Pituitary tumours

### Hormones secreted

- prolactin- 35%
- no obvious hormone, 'non-functioning', 'chromophobe' - 30%
- growth hormone - 20%
- prolactin and growth hormone - 7%
- ACTH - 7%
- others: TSH, LH, FSH - 1%

### Question 7 of 83

A 39 year-old man presents to his GP for an annual review of his type 1 diabetes. His main complaints over the last year are having several episodes of vomiting after meals and chronic constipation, as well as having loss of sensation on both of his legs up to his knees and some sensory loss in his fingertips. On further questioning, you establish there has been no weight loss or haematemesis. On examination, his HbA1c is 72 mmol/mol, blood pressure is 138/88 mmHg and his pulse is regular and 84 beats per minute. Neurological examination demonstrates a lack of proprioception up to the ankle joint and loss of sensation as described above.

What is the most appropriate symptomatic treatment for the gastrointestinal symptoms described above?

[Lansoprazole5%Omeprazole6%Metoclopramide75%Mirtazapine7%Cyclizine7%](#)

The most likely diagnosis in this scenario is gastroparesis, caused by the type 1 diabetes. Metoclopramide is the most appropriate treatment as it is a pro-kinetic antiemetic, although erythromycin and domperidone can also be used as alternatives.

## Diabetic neuropathy

NICE updated its guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs

- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

### Gastroparesis

- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

### Question 8 of 83

A 23-year-old woman with known type 1 diabetes mellitus is brought to the emergency department resus area unwell. On taking her history she mentions that she has had a cough for the past three days with fevers, and today she developed vague abdominal pain. A blood gas take on admission shows:

pH	7.21
pO <sub>2</sub>	14.8 kPa
pCO <sub>2</sub>	3.1 kPa
Bicarbonate	14 mEq/L
Base excess	-10.5 mmol/L
Na <sup>+</sup>	145 mmol/L
K <sup>+</sup>	5.3 mmol/L
Glucose	40.1 mmol/L
Lactate	2.3 mmol/L

### Urinalysis:

Leucocytes	-
Blood	-
Glucose	+++
Ketones	++++

The patient has been given 500mls of 0.9% saline as a stat bag, followed by a further 1L of 0.9% saline over 60 minutes, and her observations are as follows:

Respiratory rate	25 breaths/minute
Saturations	99% on 2L

Temperature 37.7°C  
Blood pressure 106/67 mmHg  
Heart Rate 102 beats/minute

The nurses weigh her at 60 Kg  
Her lab results are pending

Which fluid and insulin regimen would be the most appropriate at her current stage?

[1L of 0.9% Normal Saline with 20mmol of KCl added given over 2 hours + IV insulin at 6 units per hour](#)  
[42% 1L of 0.9% Normal Saline with 40mmol of KCl added given over 2 hours + IV insulin at 6 units per hour](#)  
[35% 1L of 0.9% Normal Saline with 20mmol of KCl added given over 2 hours + Sliding scale IV insulin based on capillary blood sugar readings](#)  
[8% 1L of 0.9% Normal Saline with 20mmol of KCl added given over 2 hours + 1L of 1.26% sodium bicarbonate solution over 8h + IV insulin at 6 units per hour](#)  
[7% 1L of 0.9% Normal Saline with 40mmol of KCl added given over 4 hours + IV insulin at 6 units per hour](#)  
[9%](#)

Answering this question requires knowledge of the up to date guidelines on treating diabetic ketoacidosis (see link below). There are a few key points to the new guidelines which make this question easy to answer by a process of elimination.

First is potassium replacement in fluid which is based on the patient's current potassium

**Current potassium level mmol/L Potassium replacement mmol/L of infusion solution**

>5.5	Nil
3.5-5.5	40 mmol
<3.5	senior review

Second is the rate at which fluids should be given in the early part of management, and is based on the initial blood pressure (where a systolic blood pressure of 90mmHg is a cut off for getting senior help). When the systolic blood pressure is over 90 mmHg the fluid replacement after the initial 500ml stat is as follows:

Fluid	Volume
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Finally the guidelines regarding IV bicarbonate are clear:

Adequate fluid and insulin therapy will resolve the acidosis in DKA and the use of bicarbonate is not indicated. The acidosis may be an adaptive response as it improves oxygen delivery to the

tissues by causing a right shift of the oxygen dissociation curve. Excessive bicarbonate may cause a rise in the CO<sub>2</sub> partial pressure in the cerebrospinal fluid (CSF) and may lead to a paradoxical increase in CSF acidosis. In addition, the use of bicarbonate in DKA may delay the fall in blood lactate: pyruvate ratio and ketones when compared to intravenous 0.9% sodium chloride infusion. There is some evidence to suggest that bicarbonate treatment may be implicated in the development of cerebral oedema in children and young adults.

This leaves only one possible option.

Full guidance:

<https://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/Management-of-DKA-241013.pdf>

Summary of guidance:

<https://www.diabetes.org.uk/Documents/About%20Us/Our%20views/Care%20recs/Joint%20British%20Diabetes%20Societies%20Inpatient%20Care%20Group%20-%20The%20Management%20of%20Diabetic%20Ketoacidosis%20in%20Adults%20-%20Pathway%20Poster.pdf>

## **Diabetic ketoacidosis**

Diabetic ketoacidosis may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction

Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

## **Diagnostic criteria**

**American Diabetes Association  
(2009)**

Key points

**Joint British Diabetes Societies (2013)**

Key points

### **American Diabetes Association (2009)**

- glucose > 13.8 mmol/l
- pH < 7.30
- serum bicarbonate < 18 mmol/l
- anion gap > 10
- ketonaemia

### **Joint British Diabetes Societies (2013)**

- glucose > 11 mmol/l or known diabetes mellitus
- pH < 7.3
- bicarbonate < 15 mmol/l
- ketones > 3 mmol/l or urine ketones ++ on dipstick

### **Management**

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia

### **JBDS example of fluid replacement regime for patient with a sSystolic BP on admission 90mmHg and over**

<b>Fluid</b>	<b>Volume</b>
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

### **JBDS potassium guidelines**

<b>Potassium level in first 24 hours (mmol/L)</b>	<b>Potassium replacement in mmol/L of infusion solution</b>
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

### **Complications of DKA and its treatment**

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema\*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

\* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

#### Question 9 of 83

A 47-year-old man attended his GP after checking his blood pressure at the local pharmacy. When he had it checked it was 179/102 mmHg. The GP confirmed it was high in the surgery at 186/103 mmHg. He started him on ramipril 2.5mg and titrated up to the dose to 10mg over the next few weeks. His repeat measurements showed consistently high readings so the GP added amlodipine, which had very little effect despite being tolerated at the maximum dose. After failing to get an adequate response with the addition of a third agent the GP referred the patient to the endocrine clinic.

Observations showed a blood pressure of 190/105 mmHg and a heart rate of 98 beats per minute. On examination, the man was thin with a body mass index of 23 kg/m<sup>2</sup>. His apex was diffuse and displaced with normal heart sounds. The chest was clear and abdomen was soft and non-tender with no evidence of masses or renal bruits. He was noted to have a hard, painless nodule over the thyroid gland.

The 24 hour urinary catecholamines were raised and further investigations confirmed phaeochromocytoma. He was treated medically with an alpha blocker then beta blocker whilst awaiting surgery. In this period he had further investigation into the thyroid nodule, which was a cold nodule on radionuclide scanning.

Which type of thyroid cancer would you expect this to be histologically?

[Papillary 10% Follicular 7% Anaplastic 5% Lymphoma 4% Medullary 74%](#)

This question tests your knowledge of multiple endocrine neoplasias (MEN). This patient could have MEN Type IIa or IIb, which both include phaeochromocytoma and medullary thyroid cancer.

Of all thyroid cancers, medullary thyroid cancer accounts for approximately 5% (and of these, 80% will be sporadic rather than associated with MEN).

## Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

### Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

### Further information

Type	Notes
Papillary carcinoma	<ul style="list-style-type: none"><li>• Usually contain a mixture of papillary and colloidal filled follicles</li><li>• Histologically tumour has papillary projections and pale empty nuclei</li><li>• Seldom encapsulated</li><li>• Lymph node metastasis predominate</li><li>• Haematogenous metastasis rare</li></ul>
Follicular adenoma	<ul style="list-style-type: none"><li>• Usually present as a solitary thyroid nodule</li><li>• Malignancy can only be excluded on formal histological assessment</li></ul>
Follicular carcinoma	<ul style="list-style-type: none"><li>• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.</li><li>• Vascular invasion predominates</li></ul>

Type	Notes
Medullary carcinoma	<ul style="list-style-type: none"> <li>• Multifocal disease raree</li> <li>• C cells derived from neural crest and not thyroid tissue</li> <li>• Serum calcitonin levels often raised</li> <li>• Familial genetic disease accounts for up to 20% cases</li> <li>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.</li> </ul>
Anaplastic carcinoma	<ul style="list-style-type: none"> <li>• Most common in elderly females</li> <li>• Local invasion is a common feature</li> <li>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.</li> </ul>

#### Question 10 of 83

A 59 year old gentleman with capricious type 2 diabetes mellitus is reviewed in a community diabetic clinic. Despite optimising lifestyle and diet, glycaemic control is still poor on first line oral hypoglycaemic therapy. His diabetic consultant decides to start him on dapagliflozin 10mg daily.

Which of the following is a common side effect of dapagliflozin the patient should be warned about?

[Pancytopenia3%](#)[Jaundice4%](#)[Increased likelihood of pancreatitis25%](#)[Increased likelihood of urinary infections60%](#)[Increased risk of ischaemic heart disease7%](#)

Dapagliflozin is a SGLT-2 inhibitor which causes increased renal glucose loss to control diabetic glycaemia. It may cause recurrent urinary infections due to high urinary glucose load

Since the regulation of glucose and insulin is affected by many physiological variables, there are many targets for drugs to influence glycaemic homeostasis. Older oral hypoglycaemic drugs such as the sulphonylureas (gliclazide, etc) work by directly stimulating insulin release from pancreatic beta cells, whereas biguanides like metformin inhibit glucose mobilisation from hepatic stores and improve glucose handling. Metformin is associated with lactic acidosis and sulphonylureas are associated with increased incidence of hepatitis and jaundice.

A class of oral hypoglycaemic agent known as the thiazolidinediones (pioglitazone, etc) also improve glucose processing by increasing upregulation of genes which augment glucose and fat metabolism. This occurs by stimulation of the nuclear signalling protein peroxisome proliferator-activated receptor gamma (PPAR-). Thiazolidinediones have fallen out of vogue of late due to concerns about heart failure and ischaemic heart disease.



A more novel treatment for hyperglycaemia is the use of incretins which are gastrically derived peptides which also stimulate insulin secretion from beta cells. The two main peptides of use are glucose like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) both of which synergistically stimulate beta cell insulin release and inhibit alpha cell glucagon release, causing a fall in blood glucose. Incretin drugs of this class include exenatide and liraglutide and are usually given as subcutaneous daily injections. In vivo, GLP-1 and GIP are rapidly deactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) which limits their use (although the synthetic incretin analogue drugs are not deactivated by this enzyme). Drugs which can inhibit DPP-4 are useful in controlling blood glucose since they allow physiological gut incretins to stimulate insulin release. Examples of these drugs include sitagliptin, saxagliptin, etc. Rarely DPP-4 inhibitors and PPAR- modulators can cause hepatitis, pancreatitis and pancytopenia. Previous pancreatitis is a relative contraindication to their use.

Dapagliflozin is a renal SGLT-2 (sodium glucose transporter) inhibitor which has only recently obtained UK and US licensing authority. It causes an increase in glucose excretion by the kidney to lower serum glucose concentrations. SGLT-2 is a sodium/glucose co-transporter protein in the nephrons proximal tubule which reabsorbs glucose from the renal filtrate. These drugs cause heavy urinary glucose loss and can cause recurrent urinary infections and candidiasis as well as hypoglycaemia, crystalluria and renal failure due to osmotic diuresis.

## **Diabetes mellitus: management of type 2**

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

### **Dietary advice**

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids

- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

## HbA1c targets

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

Practical examples

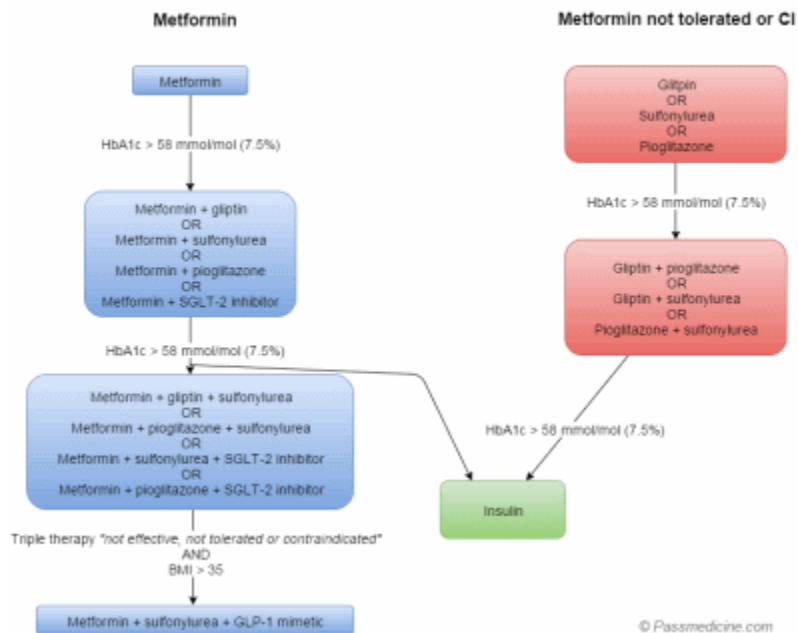
- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

## Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



### Tolerates metformin:

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  - sulfonylurea
  - gliptin
  - pioglitazone
  - SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  - metformin + gliptin + sulfonylurea
  - metformin + pioglitazone + sulfonylurea
  - metformin + sulfonylurea + SGLT-2 inhibitor
  - metformin + pioglitazone + SGLT-2 inhibitor
  - OR insulin therapy should be considered

Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
- → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or
- → BMI  $< 35$  kg/m<sup>2</sup> and for whom insulin therapy would have significant occupational implications or

weight loss would benefit other significant obesityrelated comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

### Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

### Cannot tolerate metformin or contraindicated

- if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

### Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

## Risk factor modification

### Blood pressure

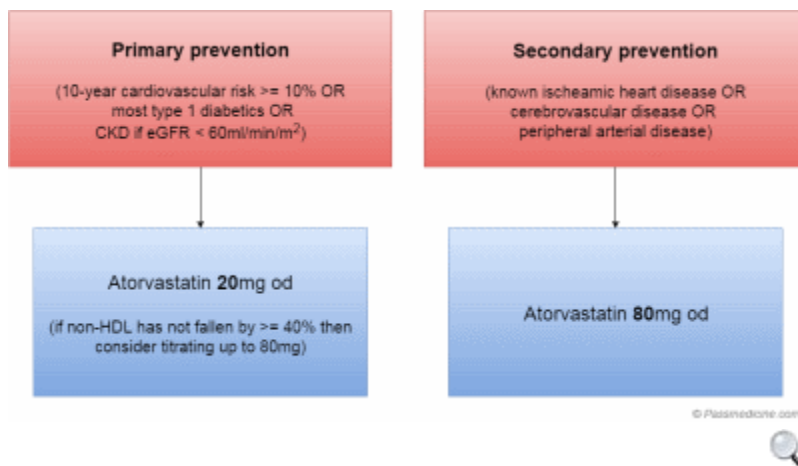
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

### Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



Graphic showing choice of statin.

\*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

### Question 1 of 73

A 50-year-old female is referred to the clinic with hypercalcaemia found coincidentally during routine investigations. On further questioning she admits that she is taking a lot of antacid preparations (for her reflux oesophagitis) and calcium and vitamin D for protection against osteoporosis as her mother and sister have osteoporosis for which they are taking alendronate.

On examination there were no relevant findings.

Investigations reveal:

Serum sodium	135 mmol/L
Serum potassium	3.5 mmol/L
Serum urea	4.2 mmol/L
Serum creatinine	77 mol/L
Serum calcium	2.8 mmol/L
Serum phosphate	0.8 mmol/L
Plasma PTH	5.4 pmol/L (0.9-5.4)
24-h urinary calcium	1.5 mmol/24hr (2.5-7.5)

What is the most likely diagnosis?

[Primary hyperparathyroidism 27%](#) [Milk- alkali syndrome 17%](#) [Hypervitaminosis D 5%](#) [Familial hypocalciuric hypercalcaemia 47%](#) [Tertiary hyperparathyroidism 4%](#)

Patients with familial benign hypocalciuric hypercalcaemia may have a normal or raised PTH. Familial hypocalciuric hypercalcaemia is an autosomal dominant disease characterized by asymptomatic hypercalcaemia with hypocalciuria and a normal PTH level. Most cases are discovered incidentally.

### **Familial benign hypocalciuric hypercalcaemia**

Familial benign hypocalciuric hypercalcaemia is a rare autosomal dominant disorder characterised by asymptomatic hypercalcaemia. It is due to a defect in the calcium-sensing receptor and a decreased sensitivity to increases in extracellular calcium.

The parathyroid hormone level is often not suppressed, as would be expected in all non-

hyperparathyroidism related cases of hypercalcaemia. This is due to the decreased sensitivity to increases in extracellular calcium.

#### Question 2 of 73

A 34-year-old man of ethnic Indian origin is reviewed in endocrinology clinic. He has type 1 diabetes. He has a twice-daily mixed insulin regime but has poor diabetic control with elevated HbA1c and high blood glucose. He wants to improve his diabetic control but is concerned about increasing his insulin dose or frequency as he is already overweight with a body mass index (BMI) of 29kg/m<sup>2</sup>.

Apart from increasing insulin, are there any other medical management options to better control his diabetes?

[No further medical treatment14% Metformin47% Gliclazide7% Acarbose22% Pioglitazone10%](#)

The correct answer is metformin. This is a patient with poorly controlled type 1 diabetes. Of importance to this case, he is also overweight and is of ethnic Indian origin. Increasing insulin doses is seldom popular due to the side effects. NICE recommends that in overweight people of Indian origin metformin is an alternative to increasing insulin and may be helpful, especially as it would not lead to further weight increase.

Source:

'Type 1 diabetes in adults: diagnosis and management' Clinical guideline [NG17]. The National Institute for Health and Care Excellence, August 2015.

## **Insulin therapy**

Insulin therapy revolutionised the management of diabetes mellitus when it was developed in the 1920's. It is still the only available treatment for type 1 diabetes mellitus (T1DM) and is widely used in type 2 diabetes mellitus (T2DM) where oral hypoglycaemic agents fail to gain adequate control.

It can sometimes seem daunting to understand the various types of insulin but it is important you have a basic grasp to avoid potential harm to patients.

## **Classification of insulin**

By manufacturing process

- porcine: extracted and purified from pig pancreas
- human sequence insulin: either produced by enzyme modification of porcine insulin (emp) or biosynthetically by recombinant DNA using bacteria (crb, prb) or yeast (pyr)
- analogues

By duration of action

	<b>Onset</b>	<b>Peak</b>	<b>Duration</b>
<b>Rapid-acting insulin analogues</b>	5 mins	1 hour	3-5 hours
<b>Short-acting insulin</b>	30 mins	3 hours	6-8 hours
<b>Intermediate-acting insulin</b>	2 hours	5-8 hours	12-18 hours
<b>Long-acting insulin analogues</b>	1-2 hours	Flat profile	Up to 24 hours
<b>Premixed preparations</b>	-	-	-

Patients often require a mixture of preparations (e.g. both short and long acting) to ensure stable glycaemic control throughout the day.

Rapid-acting insulin analogues

- the rapid-acting human insulin analogues act faster and have a shorter duration of action than soluble insulin (see below)
- may be used as the bolus dose in 'basal-bolus' regimes (rapid/short-acting 'bolus' insulin before meals with intermediate/long-acting 'basal' insulin once or twice daily)
- insulin aspart: NovoRapid
- insulin lispro: Humalog

Short-acting insulins

- soluble insulin examples: Actrapid (human, pyr), Humulin S (human, prb)
- may be used as the bolus dose in 'basal-bolus' regimes

Intermediate-acting insulins

- isophane insulin
- many patients use isophane insulin in a premixed formulation with

Long-acting insulins



- insulin detemir (Levemir): given once or twice daily
- insulin glargine (Lantus): given once daily

#### Premixed preparations

- combine intermediate acting insulin with either a rapid-acting insulin analogue or soluble insulin
- Novomix 30: 30% insulin aspart (rapid-acting), 70% insulin aspart protamine (intermediate-acting)
- Humalog Mix25: 25% insulin lispro (rapid-acting), 75% insulin lispro protamine (intermediate-acting); Humalog Mix50: 50% insulin lispro, 50% insulin lispro protamine
- Humulin M3: biphasic isophane insulin (human, prb) - 30% soluble (short-acting), 70% isophane (intermediate-acting)
- Insuman Comb 15: biphasic isophane insulin (human, prb) - 30% soluble (short-acting), 70% isophane (intermediate-acting)

#### Administration of insulin

The vast majority of patients administer insulin subcutaneously. It is important to rotate injection sites to prevent lipodystrophy. Insulin pumps are available ('continuous subcutaneous insulin infusions') which delivers a continuous basal infusion and a patient-activated bolus dose at meal times.

Intravenous insulin is used for patients who are acutely unwell, for example with diabetic ketoacidosis. Inhaled insulin is available but not widely used and oral insulin analogues are in development but have considerable technical hurdles to clear.

#### Question 3 of 73

An 82-year-old female presents to clinic with her daughter complaining of a four month of history of urinary incontinence. She explains that she has not previously had problems with continence. Her only past medical history include hypertension and angina. Now, she is incontinent of urine only when she laughs or coughs. At times, she reports sudden urges to urinate at all times during the day, resulting in a leak when she is unable to reach the toilet in time. This is significantly impacted on her sleep as well as it is increasingly frequent at night. The patient has reduced her caffeine intake already and has commenced 'bladder training' recommended by her GP. What additional management would you commence?

[Pelvic floor exercises only16%](#)[Pelvic floor exercises and tolterodine54%](#)[Pelvic floor exercises and duloxetine21%](#)[Pelvic floor exercises and desmopressin7%](#)[Long term urinary catheter3%](#)

The question concentrates on the management of an elderly patient with mixed stress incontinence and overactive bladder syndrome. In the context of mixed urinary incontinence, pharmacological therapies should be offered in addition to conservative therapies such as pelvic floor exercises. A long-term catheter in whom persistent incontinence causes skin wounds, the patient requires such significant care that continuous changing of bed linen and clothes would be required, chronic retention with a risk of renal impairment (and inability to self-catheterise) or if the patient opts for the catheterisation. The 2013 NICE guidelines recommends first line pharmacological treatment for mixed incontinence or overactive bladder syndrome alone is either tolterodine, oxybutynin or darifenacin<sup>1</sup>. Duloxetine should only be used if the patient does not tolerate first line therapy and is not a candidate for surgery. Desmopressin can reduce nocturia. However, its effects in platelet activation contradicts its use in ischaemic heart disease.

1. NICE Guideline 171. Urinary incontinence. The management of urinary incontinence in women. September 2013

## **Urinary incontinence**

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

### **Risk factors**

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

### **Classification**

- overactive bladder (OAB)/urge incontinence: due to detrusor over activity
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement

### **Initial investigation**

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinic is first-line. NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation). Immediate release oxybutynin should, however, be avoided in 'frail older women'

If stress incontinence is predominant:

- pelvic floor muscle training: NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures

#### Question 4 of 73

A 75-year-old man with a history of high blood pressure, type 2 diabetes and hypercholesterolaemia was admitted to the emergency department with confusion. His daughter states that this has come on slowly over the last week and prior to this he had no memory problems. He currently takes metformin, ramipril, amlodipine and atorvastatin.

On examination, he smells strongly of urine and his mucous membranes appear dry. His abbreviated mental test score is 7 out of 10 and he is oriented in person but not in place or time. His heart rate is 95 per minute and his blood pressure is 105/62 mmHg. His chest is clear and has a soft ejection systolic murmur which does not radiate. His jugular venous pressure is not visible and he has mild ankle oedema. He has diffuse tenderness in the lower abdomen with no peritonism and normal bowel sounds. He has no focal neurology.

Investigation results are as follows:

Chest x-ray: Clear lung fields.

Urine dip:

Glucose +++  
Blood +  
Protein +  
Leucocytes +  
Nitrites +  
Ketones +

Venous blood gas:

pH 7.43  
BE - 1.5 mmol/l  
HCO<sub>3</sub> 23 mmol/l  
Glucose 34 mmol/l  
Lactate 2.5 mmol/l

Full blood count:

Hb 120 g/l  
Platelets 445 \* 10<sup>9</sup>/l  
WBC 13 \* 10<sup>9</sup>/l

Renal function:

Na<sup>+</sup> 151 mmol/l  
K<sup>+</sup> 5 mmol/l  
Urea 10 mmol/l  
Creatinine 137 µmol/l  
Glucose 32 mmol/l  
Ketones 2 mmol/l

Which would be the most appropriate initial resuscitation measure?

[0.45% saline8%0.9% saline57%Fixed rate insulin and 0.9% saline21%Hartmann's4%Sliding scale insulin and 0.9% saline10%](#)

This gentleman has hyperosmolar hyperglycaemic state (HHS), likely precipitated by urinary tract infection and his pre-existing diabetes.

According to the Joint British Diabetes Society Guidelines for HHS, 0.9% saline is the recommended initial resuscitation fluid, aiming for 3-6 litres positive at 12 hours. This should only be switched to 0.45% saline if osmolality is declining despite positive fluid balance. Fixed rate insulin should only be added if glucose fails to fall with fluid.

Reference: Joint British Diabetes Societies Inpatient Care Group. The management of hyperosmolar hyperglycaemic state (HHS) in adults with diabetes. 2012.

## Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality  $>320 \text{ mosmol/kg}$
- Hyperglycaemia  $>30 \text{ mmol/L}$  with  $\text{pH} >7.3$ , bicarbonate  $>15 \text{ mmol/L}$  and no significant ketonuria  $<3 \text{ mmol/L}$

### Question 5 of 73

A 62-year-old male, recently emigrated from India, presents with 5 day history of feeling generally unwell. His niece, who has accompanied him to hospital, denies a history of recent productive cough, diarrhoea or vomiting or dysuria. Her uncle had been gradually increasingly malaised over the past 5 days and not eating and drinking well. He has no known past medical history. On examination, he has dry mucous membranes and cool peripheries, his JVP is +1cm above the angle of Louis. Heart sounds, chest and abdomen are unremarkable. Urine dip and chest radiograph are awaited. His blood tests are as follows:

WBC  $16 \times 10^9/\text{l}$   
Neutrophils  $14.8 \times 10^9/\text{l}$

$\text{Na}^+$   $152 \text{ mmol/l}$   
 $\text{K}^+$   $3.7 \text{ mmol/l}$   
Urea  $22 \text{ mmol/l}$   
Creatinine  $208 \mu\text{mol/l}$   
CRP  $38 \text{ mg/l}$   
Glucose  $38 \text{ mmol/l}$   
Ketones  $2.8 \text{ mmol/l}$

Arterial blood gases:

pH 7.31  
PaO<sub>2</sub> 20.2 kPa  
PaCO<sub>2</sub> 3.0 kPa  
Bicarbonate 16 mmol/l  
Lactate 4 mmol/l

What is the unifying diagnosis?

[Diabetic ketoacidosis \(DKA\)22%](#)[Lactic acidosis5%](#)[Hyperosmolar hyperglycaemic state \(HHS\)67%](#)[Urinary tract sepsis3%](#)[Chest sepsis3%](#)

This patient has presented with dehydration and non-specific symptoms and a diagnosis difficult to diagnose clinically. However, his biochemistry is diagnostic: calculation of his osmolality,  $(2[Na + K] + urea + glucose)$  reveals an osmolality greater 371.4mosmol/kg. He is likely to present acutely with undiagnosed type 2 diabetes mellitus and a diagnosis of HHS, previously known as HONK.

There is no evidence to suggest uro or chest sepsis but an infectious underlying decompensating trigger should be considered with a prescription of broad spectrum antibiotics. Although lactate is mildly raised, this is likely secondary to intravascular dehydration and hypoperfusion of internal organs. Lactic acidosis alone does not account for the full biochemical picture. Ketones are present and the patient is mild acidotic. However, be aware that neither is sufficiently significant for a diagnosis of DKA.

## **Hyperosmolar hyperglycaemic state**

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality >320mosmol/kg
- Hyperglycaemia >30 mmol/L with pH >7.3, bicarbonate >15mmol/L and no significant ketonenaemia <3mmol/L

You review a 28-year-old woman who is 26 weeks pregnant. She has just had a routine oral glucose tolerance test as her BMI is 34 kg/m<sup>2</sup>. The following results were obtained:

**Time (hours) Blood glucose (mmol/l)**

0	7.4
2	11.2

There have been no other antenatal problems and her anomaly scan was normal. What is the most appropriate action?

[Repeat oral glucose tolerance test in 4 weeks7%](#)[Start metformin + advice about diet / exercise + self-monitor glucose levels29%](#)[Advice about diet / exercise + self-monitor glucose levels22%](#)[Start insulin + advice about diet / exercise + self-monitor glucose levels39%](#)[Reassure results within normal limits4%](#)

NICE have recently changed their gestational diabetes guidelines. Insulin should be started in the fasting glucose is  $\geq 7$  mmol/l. Aspirin should also be considered given the increased risk of pre-eclampsia.

### **Pregnancy: diabetes mellitus**

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates around 1 in 40 pregnancies. NICE updated the guidance in 2015

Risk factors for gestational diabetes

- BMI of  $> 30$  kg/m<sup>2</sup>
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- women who've previously had gestational diabetes: oral glucose tolerance test (OGTT) should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

## Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is  $\geq 5.6$  mmol/l
- 2-hour glucose is  $\geq 7.8$  mmol/l

## Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about selfmonitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is  $< 7$  mmol/l a trial of diet and exercise should be offered
- if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
- if glucose targets are still not met insulin should be added to diet/exercise/metformin
- if at the time of diagnosis the fasting glucose level is  $\geq 7$  mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

## Management of pre-existing diabetes

- weight loss for women with BMI of  $> 27$  kg/m<sup>2</sup>
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

## Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l



### Question 1 of 63

A 65-year-old Muslim man with type II diabetes on metformin (500mg three times a day) comes to your endocrine clinic. He is about to start fasting between sunrise and sunset for Ramadan. He will typically eat a light meal before sunrise (Suhoor) and a large meal at sunset (Iftar).

How would you advise this gentleman in respect to his metformin prior to the large meal at sunset?

[Change to a sulphonylurea3% Stop metformin4% Take 1.5g metformin before the large meal at sunset10% Take 500mg metformin before the large meal at sunset8% Take 1g metformin before the large meal at sunset75%](#)

This patient will still require metformin and therefore it is not appropriate to stop it.

The total daily dose of metformin should be split:

- One-third before sunrise (Suhoor) (500mg)
- Two-thirds after sunset (Iftar) (1g)

There is no need to change to a sulphonylurea if his blood glucose levels are controlled on metformin alone.

### **Diabetes mellitus: Ramadan**

We know that type 2 diabetes mellitus is more common in people of Asian ethnicity and a significant proportion of those patients in the UK will be Muslim. The BMJ published an excellent and comprehensive review of this issue in 2010<sup>1</sup>.

It is important that we can give appropriate advice to Muslim patients to allow them safely observe their fast. This is particularly important from 2014 as Ramadan is due to fall in the long days of the summer months for several years henceforth.

Clearly it is a personal decision whether a patient decides to fast. It may however be worthwhile exploring the fact that people with chronic conditions are exempt from fasting or may be able to delay fasting to the shorter days of the winter months. It is however known that many Muslim patients with diabetes do not class themselves as having a chronic/serious condition which

should exempt them from fasting. Around 79% of Muslim patients with type 2 diabetes mellitus fast Ramadan<sup>2</sup>. There is an excellent patient information leaflet from Diabetes UK and the Muslim Council of Britain which explores these options in more detail.

If a patient with type 2 diabetes mellitus does decide to fast:

- they should try and eat a meal containing long-acting carbohydrates prior to sunrise (Suhoor)
- patients should be given a blood glucose monitor to allow them to check their glucose levels, particularly if they feel unwell
- for patients taking metformin the expert consensus is that the dose should be split one-third before sunrise (Suhoor) and two-thirds after sunset (Iftar)
- expert consensus also recommends switching once-daily sulfonylureas to after sunset. For patients taking twice-daily preparations such as gliclazide it is recommended that a larger proportion of the dose is taken after sunset
- no adjustment is needed for patients taking pioglitazone

1. Management of people with diabetes wanting to fast during Ramadan BMJ 2010;340:c3053

2. Salti I et al. Results of the Epidemiology of Diabetes and Ramadan (EPIDIAR) study. Diabetes Care 2004;27:2306-11.

#### Question 2 of 63

A 38-year-old woman is referred by her GP for management of Graves' disease, diagnosed by the presence of a goitre, suppressed thyroid stimulating hormone, and presence of thyroid antibodies on screening. She has no past medical history of note, drinks 10 units of alcohol per week and smokes 20 cigarettes per day. On examination her blood pressure is 112/88 mmHg, pulse is 89 beats per minute and regular, she has a fine tremor. There is a smooth goitre and marked proptosis.

Which of the following has the greatest negative impact on prognosis of her thyroid eye disease?

[Alcohol consumption5%](#)[Cigarette smoking76%](#)[DR4 HLA type6%](#)[LATS titre6%](#)[Use of block replace therapy7%](#)

A systematic review published in 2006 has confirmed the strong link between cigarette smoking and thyroid eye disease. Across 15 studies a strong association between thyroid eye disease in patients with Graves' disease and smoking was established, with an odds ratio of up to 20 for thyroid eye disease in current smokers vs non-smokers who have Graves'.

<http://www.ncbi.nlm.nih.gov/pubmed/16980921>

Block replace therapy establishes stable control of thyroid function, and is actually associated

with reduced incidence of thyroid eye disease because thyroxine is consistently in the normal range. Alcohol consumption within the recommended safe limits may actually reduce the severity of thyroid eye disease in Graves'. Thyroid eye disease is primarily driven by pathogenic T cells, as such it isn't closely related to LATs titre. HLA DR4 is more strongly associated with Type 1 diabetes, rheumatoid arthritis and autoimmune hepatitis than with thyroid disease.

## **Thyroid eye disease**

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

### **Pathophysiology**

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

### **Prevention**

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

### **Features**

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

### **Management**

- topical lubricants may be needed to help prevent corneal inflammation caused by exposure

- steroids
- radiotherapy
- surgery

### **Monitoring patients with established thyroid eye disease**

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

### Question 1 of 63

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Question 3 of 63

A 72-year-old female presents with 5 days of general decline following a recent urinary tract infection, treated with oral antibiotics in the community by the GP. She is known to be a type 2

diabetic, diagnosed 28 years ago and insulin dependent for the past 6 years. She is normally on 46 units Lantus, 23 units TDS Novorapid. On examination, she is not orientated in time or place, GCS 14/15. She has no focal neurology, chest and cardiovascular auscultation are unremarkable. You demonstrate suprapubic tenderness on deep palpation but the abdomen is otherwise soft and non-tender, bowel sounds are present. She appears extremely dehydrated: her mucous membranes are dry, peripheries cool with capillary refill time of 4 seconds and JVP +1 cm above the angle of Louis. Her blood sugar is 31mmol/L and a venous blood gas demonstrates pH 7.22, lactate 2 mmol/l, ketones 5 mmol/l. A urine dip is awaited. What is the most likely diagnosis?

[Hyperglycaemic hyperketotic state 28% Hyperglycaemia secondary to poor medical compliance during recent acute illness 6% Urosepsis secondary to inadequately treated UTI 7% Diabetic ketoacidosis 55% Dehydration secondary to poor oral intake 4%](#)

The patient is acidotic with ketones >3 mmol/l demonstrated, on a background of known insulin dependence. Although she is known to be a type 2 diabetic, it should be remembered that both types of diabetics can present as DKA, particularly advanced T2 DM who produce little to no endogenous insulin and are hence unable to shut down ketogenesis. Treatment should be as per DKA protocols, with intravenous fluids, fixed rate insulin infusion @ 0.1 unit/kg/hour, thromboprophylaxis, broad spectrum antibiotics and appropriate K<sup>+</sup> replacement with insulin 1.

## **Diabetic ketoacidosis**

Diabetic ketoacidosis may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction

### **Features**

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

### **Diagnostic criteria**

**American Diabetes Association  
(2009)**

**Joint British Diabetes Societies (2013)**

## **American Diabetes Association (2009)**

### Key points

- glucose > 13.8 mmol/l
- pH < 7.30
- serum bicarbonate < 18 mmol/l
- anion gap > 10
- ketonaemia

## **Joint British Diabetes Societies (2013)**

### Key points

- glucose > 11 mmol/l or known diabetes mellitus
- pH < 7.3
- bicarbonate < 15 mmol/l
- ketones > 3 mmol/l or urine ketones ++ on dipstick

### Management

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia

### **JBDS example of fluid replacement regime for patient with a sSystolic BP on admission 90mmHg and over**

<b>Fluid</b>	<b>Volume</b>
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

### **JBDS potassium guidelines**

<b>Potassium level in first 24 hours (mmol/L)</b>	<b>Potassium replacement in mmol/L of infusion solution</b>
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

### Complications of DKA and its treatment

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema\*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

\* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

#### Question 5 of 63

A 33-year-old female is brought into the emergency department as a stand-by. She has felt unwell for the past 2 weeks. She describes lethargy, light-headedness and occasional shortness of breath. More recently she developed urinary frequency and dysuria. She received a domiciliary visit from her general practitioner 2 days ago and was prescribed trimethoprim for a possible urinary tract infection.

On arrival, she appears pale and clammy. Her peripheries are cold. Her observations reveal oxygen saturations of 94% on air, respiratory rate 28/min, heart rate 117/min, blood pressure 65/30 mmHg.

She has a past medical history of type 1 diabetes, uterine fibroids and hypothyroidism.

Initial investigations reveal:

White cell count	17.8 *10 <sup>9</sup> /l
Haemoglobin	97 g/l
Mean cell volume (MCV)	103.7 fL
Sodium	134 mmol/l
Potassium	4.9 mmol/l
Urea	7.0 mmol/l
Creatinine	120 µmol/l
Bilirubin	45 µmol/l
Alanine transaminase (ALT)	1051 U/l
Albumin	16 g/l



C-reactive protein (CRP) 71 mg/dL  
Glucose 9.1 mmol/l

Urinalysis: ++protein, ++blood, +++leukocytes, ++nitrites, trace ketones

She is given intravenous fluids. Her blood pressure is 82/45 mmHg after a total of 3 litres of fluids. She is started on intravenous amoxicillin and gentamicin.

What is the next step in her management?

[1000mls intravenous colloid fluid 8% Intravenous hydrocortisone 61% Intravenous noradrenaline 16% Intravenous albumin 9% Intravenous meropenem 5%](#)

This patient has an autoimmune diathesis: she has type 1 diabetes and hypothyroidism. Her macrocytic anaemia also raises the possibility of undiagnosed pernicious anaemia. She is therefore at very high risk of primary adrenal insufficiency (Addison's Disease). IV hydrocortisone is a potentially life-saving treatment and should be given immediately. It is not contra-indicated in the presence of sepsis. Her biochemistry is not classical for Addison's, however, this does not exclude the diagnosis. Her abnormal LFTs are in keeping with a shocked liver. Intensive care review should be sought and she may well require inotropes but treatment of potential adrenal insufficiency is the immediate priority.

## **Addisonian crisis**

### **Causes**

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococemia)
- steroid withdrawal

### **Management**

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

- Question 6 of 63
- A 55-year-old female has noticed an enlarging neck lump and comes for review with you. Her TSH is low. Apart from the large goitre, there were no other significant findings on physical examination. What is the best next test to performed?
- [Anti-TSH antibodies24%Thyroid US37%Thyroid Technetium scan30%Thyroid nodule biopsy6%Thyroidectomy3%](#)

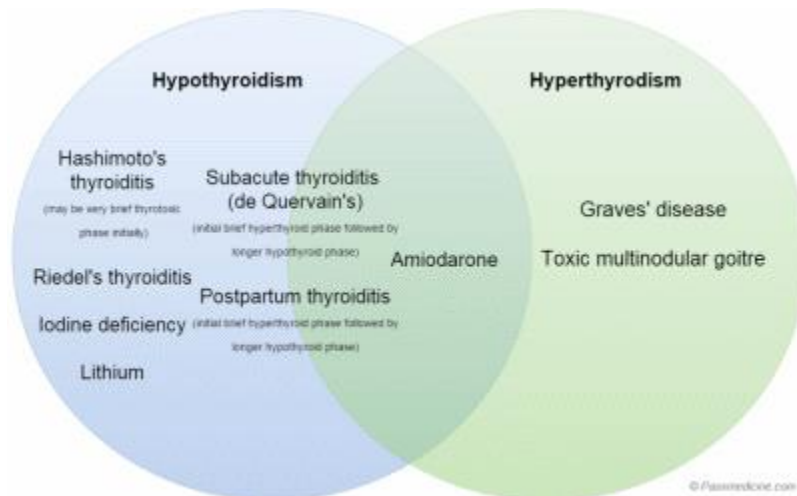
The underlying diagnosis is that of a toxic-goitre (low TSH) due to a toxic adenoma. The concern is always that the goitre may be carcinogenic. To rule carcinogenesis out a thyroid technetium scan can be done. If the technetium scan shows a 'hot' nodule, then cancer can be ruled out because it is exceedingly rare that a hot nodule is cancer. Thus an over functioning thyroid nodule is diagnosed.

A toxic adenoma occurs due to somatic mutations of the TSH receptor gene that confers autonomous hyperactivity to that thyroid tissue. It responds will to radioiodine ablation or surgical removal.

- **Thyroid function tests**

The interpretation of thyroid function tests is usually straightforward:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	In T3 thyrotoxicosis the free T4 will be normal
Primary hypothyroidism (primary atrophic hypothyroidism)	High	Low	
Secondary hypothyroidism	Low	Low	Replacement steroid therapy is required prior to thyroxine
Sick euthyroid syndrome*	Low**	Low	Common in hospital inpatients T3 is particularly low in these patients
Subclinical hypothyroidism	High	Normal	
Poor compliance with thyroxine	High	Normal	
Steroid therapy	Low	Normal	



- Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.
- - \*now referred to as non-thyroidal illness
  - \*\*TSH may be normal in some cases

#### Question 8 of 63

A 19-year-old gentleman with a background history of asthma presents to the Emergency Department complaining of leg weakness and the inability to walk. He had run a marathon the day before. On examination, there is 3/5 weakness of the leg extensors bilaterally. Tone, reflexes and coordination are unimpaired and plantars are downgoing bilaterally. Straight leg raise and sensation to light touch and pain stimulus are unimpaired.

Blood tests show the following:

Hb	13.4g/dl
WBC	$6.2 \times 10^9/l$
Na <sup>+</sup>	136mmol/l
K <sup>+</sup>	2.9mmol/l
Urea	6.8mmol/l
Creatinine	104μmol/l

What is the most appropriate treatment in this case?

[Oral potassium and encourage bed rest33%](#)  
[Hourly forced vital capacity measurements and plasma exchange4%](#)  
[Oral potassium and encourage gentle exercise51%](#)  
[Hourly forced vital capacity measurements and IV immunoglobulin7%](#)  
[Plasma exchange and oral potassium supplementation6%](#)

Hypokalaemic periodic paralysis is a rare autosomal dominant periodic paralysis but can also occur as a result of a spontaneous mutation (a third of cases have no family history). Attacks often occur in the morning with a history of strenuous exercise or a high carbohydrate meal the day before or may be provoked by stress eg. infections, lack of sleep. Weakness can range from an isolated muscle group to generalised weakness and tends to affect proximal muscles first.

Serum potassium decreases during attacks but may not necessarily fall below the normal range (3.5 -5mmol/l).

The mainstay of treatment for an acute attack is oral potassium supplementation and encouragement of gentle exercise. Intravenous potassium is reserved for those unable to swallow or with cardiac arrhythmias. Acetazolamide or dichlorphenamide are used as first-line prophylactic agents.

### **Hypokalaemic periodic paralysis**

Hypokalaemic periodic paralysis is a rare autosomal dominant disorder characterised by episodes of paralysis, typically occur at night. The underlying defect is a mutation in muscle voltage-gated calcium channels. Attacks may be precipitated by carbohydrate meals

#### **Management**

- lifelong potassium supplementation

#### **Question 9 of 63**

A 44-year-old woman is admitted to hospital complaining of a swollen breast for three days. She is otherwise well, having no medical problems. She is diagnosed by the surgical team with a breast abscess, which is drained and she is started on antibiotic treatment. Before being discharged, she is found to have elevated corrected calcium (2.79 mmol/L) and elevated parathyroid hormone (9.5 pmol/L).

She is reviewed by the endocrine team. She does not have any symptoms apart from those related to her breast abscess, and additional examination is unremarkable. Further tests are requested, showing that vitamin D levels are normal, 24-hour urine calcium is normal, and a DEXA scan is normal as well. She is advised to see her GP for annual blood tests for calcium levels and renal function.

She is diagnosed with primary hyperparathyroidism. What additional investigation should be used to monitor her?

[24-hour urine calcium annually14%Breast ultrasound annually6%Abdominal X-ray annually10%Abdominal ultrasound every three years12%DEXA scan every one to two years58%](#)

The correct answer is a DEXA scan. This patient has been incidentally found to have primary hyperparathyroidism and has no evidence of indications for parathyroidectomy. Monitoring should include renal function and DEXA scanning to identify any decline in renal function, worsening hypercalcaemia or osteoporosis. Any of these changes would be indications for surgery. Abdominal X-rays and ultrasound scanning may be useful in the acute setting to detect renal stones but are not recommended as monitoring. Urinary calcium useful at diagnosis to exclude hypocalciuric hypercalcaemia.

Source:

'Hypercalcaemia.' Clinical Knowledge Summaries. National Institute for Health and Care Excellence, Dec. 2014.

## **Primary hyperparathyroidism**

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Features - 'bones, stones, abdominal groans and psychic moans'

- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis

- bone pain/fracture
- renal stones
- depression
- hypertension

#### Associations

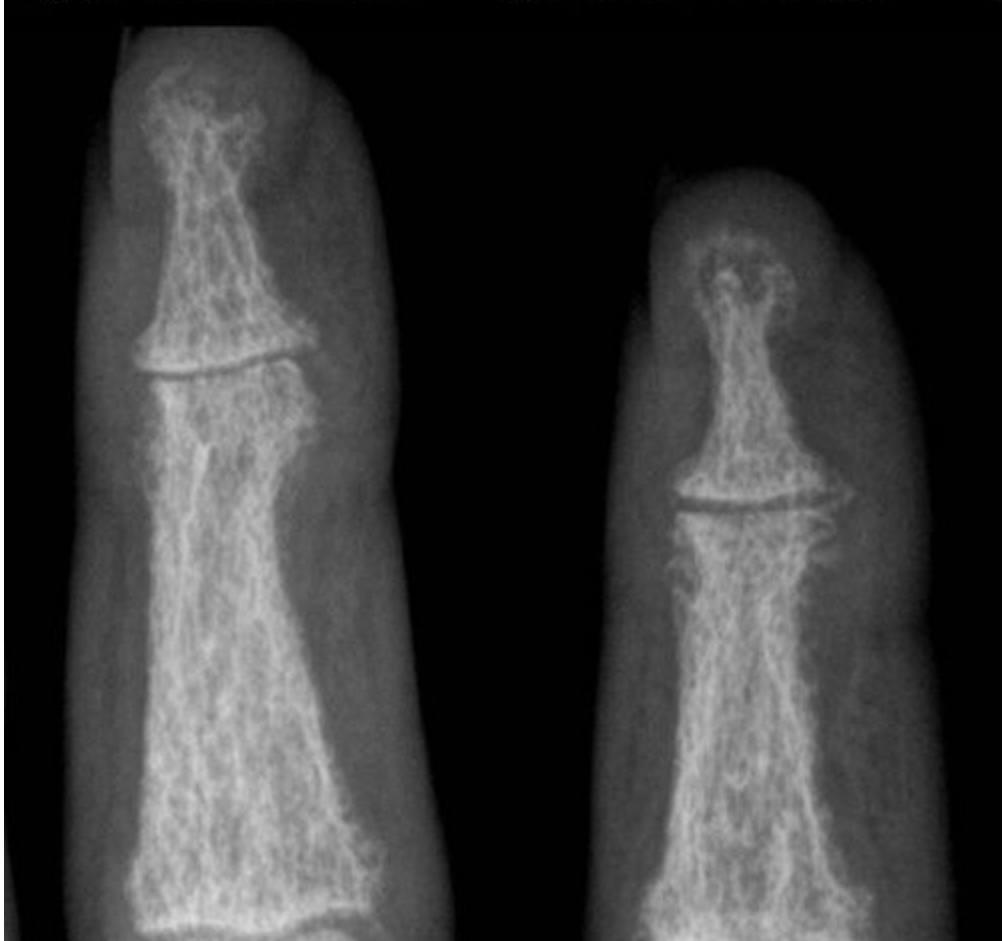
- hypertension
- multiple endocrine neoplasia: MEN I and II

#### Investigations

- raised calcium, low phosphate
- PTH may be raised or normal
- technetium-MIBI subtraction scan

#### Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- calcimimetic agents such as cinacalcet are sometimes used in patients who are unsuitable for surgery





Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

### Question 10 of 63

A 30-year-old woman with a history of type 1 diabetes presents to the Emergency department with nausea and vomiting coupled with increased urinary frequency over the past 3 days. She has been progressively losing weight and reducing her insulin dose after starting empagliflozin prescribed to help her lose weight and reduce glucose fluctuations. She also admits to taking a Chinese herbal remedy for weight control. Blood pressure is 100/70 mmHg, pulse is 88 beats per minute. pH is 7.25, glucose is 8.1 mmol/l, urine testing reveals ketones +++

Which of the following is the most likely diagnosis?

[Empagliflozin related nephrotoxicity10%](#)[Hyperosmolar non-ketotic state5%](#)[Normoglycaemic ketoacidosis57%](#)[Starvation ketoacidosis22%](#)[Urinary sepsis6%](#)

Hyperosmolar non-ketotic state is associated with marked hyperglycaemia and no ketosis. Starvation ketosis results in the formation of urinary ketones, but pH remains normal.

<http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm>

### **Normoglycaemic ketoacidosis**

Normoglycaemic ketoacidosis is increasingly recognised as a consequence of SGLT-2 inhibitor therapy in type 2 diabetes, and now more and more in patients with type 1 diabetes who are prescribed the drug off-license. The reason is thought to be that spilling of glucose into the urine leads to a reduction in plasma glucose and patients back off on insulin dose. They are then underdosed with respect to insulin, and SGLT-2 inhibitors also promote a rise in glucagon, which drives lipid oxidation and can further worsen the risk of ketoacidosis.

The problem can be avoided potentially by reducing the dose of the SGLT-2 inhibitor as patients reach blood glucose target.



### Question 1 of 54

A 79-year-old lady with a body mass index of 31 kg/m<sup>2</sup> attends clinic complaining of increasing tiredness. She is found to have a random glucose reading of 15.5 mmol/L and a recent HbA1c of 7.5%. She is currently on metformin 1g twice daily and recently stopped gliclazide due to hypoglycaemic episodes.

Which drug therapy should be added next to further control her glucose readings?

[Sitagliptin58% Insulin4% Glimepiride5% Liraglutide16% Canagliflozin17%](#)

This patient has poorly controlled type 2 diabetes mellitus given her random blood glucose reading of 15 mmol/L and HbA1c of 7.5%. Her current treatment with metformin is suitable given her current BMI in keeping with obesity. However, she is having significant hypoglycaemic episodes with gliclazide (sulfonylurea).

Therefore the next best agent to add is sitagliptin (DPP 4 inhibitor). Sitagliptin is recommended as a second agent alongside metformin (first line) when blood glucose control is inadequate (i.e. HbA1c > or equal to 6.5%) and a sulfonylurea is contraindicated or not tolerated (e.g. hypoglycaemia). Sitagliptin would be preferable in this instance to a thiazolidinedione (pioglitazone) as further weight gain would be undesirable.

Glimepiride is a longer acting second generation sulfonylurea drug and would not be suitable due to existing problems with hypoglycaemia.

Liraglutide (long-acting glucagon-like peptide 1 receptor agonist) can be considered in patients with a raised BMI if combinations of metformin, sulfonylurea, DPP 4 inhibitor and a thiazolidinedione are not tolerated or either drug is contraindicated.

Canagliflozin (sodium glucose co-transporter inhibitor) can be given as second-line agent with metformin if a sulfonylurea is contraindicated or not tolerated. It can also be given as a third agent in addition to metformin and a sulfonylurea or thiazolidinediones. The reported side effects of this drug are hypoglycaemia when used in combination with insulin or a sulfonylurea, vaginal candidiasis, urinary tract infection, polyuria and urinary frequency. Insulin should be considered with uncontrolled hyperglycaemia despite treatment with dual or triple oral hypoglycaemic agents.

## Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:

- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

#### Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

#### HbA1c targets

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

#### Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)

## Management of T2DM

Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)

## HbA1c target

53 mmol/mol  
(7.0%)

### Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

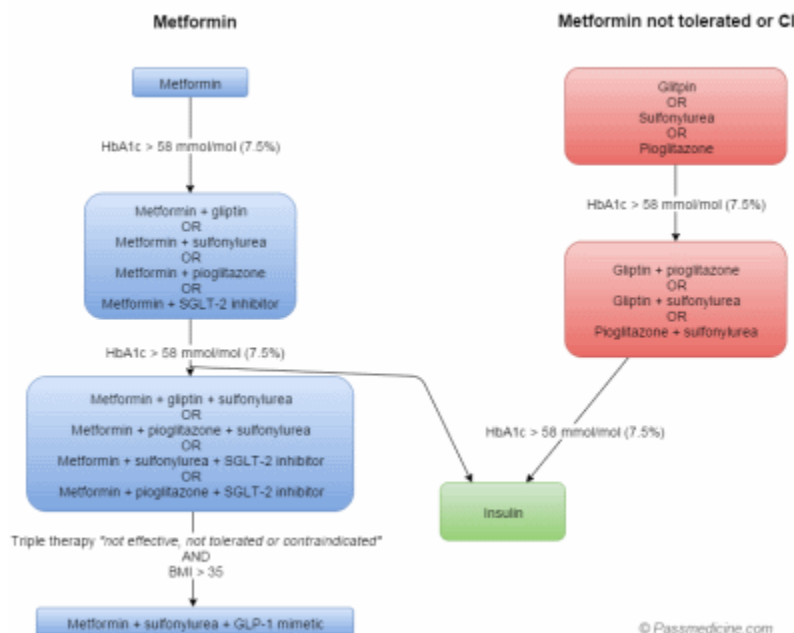
## Management of T2DM

## HbA1c target

Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%) 53 mmol/mol (7.0%)

### Drug treatment

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:



### **Tolerates metformin:**

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
  - → SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
  - → metformin + gliptin + sulfonylurea
  - → metformin + pioglitazone + sulfonylurea
  - → metformin + sulfonylurea + SGLT-2 inhibitor
  - → metformin + pioglitazone + SGLT-2 inhibitor
  - → OR insulin therapy should be considered

### **Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)**

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
  - → BMI  $\geq 35$  kg/m<sup>2</sup> and specific psychological or other medical problems associated with obesity or
  - → BMI  $< 35$  kg/m<sup>2</sup> and for whom insulin therapy would have significant occupational implications or

weight loss would benefit other significant obesityrelated comorbidities

- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

### **Practical examples**

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

### **Cannot tolerate metformin or contraindicated**

- if the HbA1c rises to 48 mmol/mol (6.5%)\* on lifestyle interventions, consider one of the following:
  - → sulfonylurea
  - → gliptin
  - → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
  - → gliptin + pioglitazone
  - → gliptin + sulfonylurea
  - → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

### Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: *'Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

### Risk factor modification

#### Blood pressure

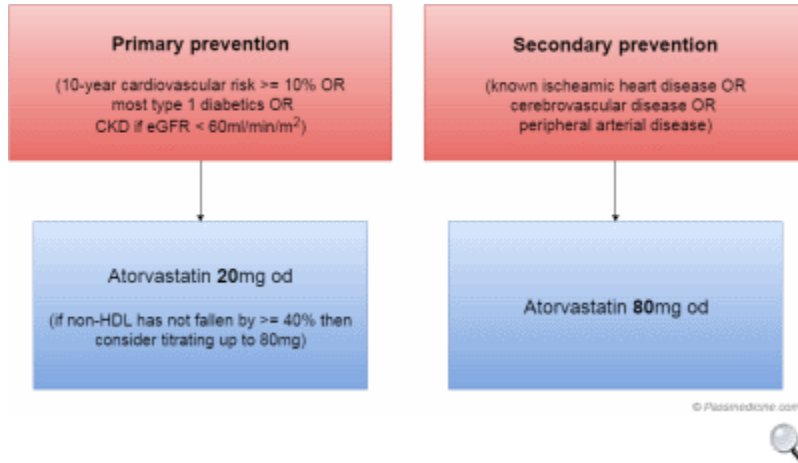
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

#### Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

#### Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on



Graphic showing choice of statin.

\*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

#### Question 2 of 54

A 55-year-old man was seen in the Emergency Department after a fainting episode. He describes a history of fatigue and nausea. His past medical history includes type 2 diabetes mellitus and HIV infection and he admits that he has not been compliant with any medications, including his anti-retroviral therapy.

On examination, his pulse was 65 beats per minute and regular, blood pressure 90/62 mmHg and respiratory rate 26 breaths per minute.

#### Investigations:

Haemoglobin	14.0 g/dL (13.0-18.0)
White cell count	$4 \times 10^9/L$ (4-11)
Platelets	$150 \times 10^9/L$ (150-400)
Sodium	130 mmol/L (135-145)
Potassium	5.8 mmol/L (3.5-5.0)
Creatinine	80 $\mu\text{mol/L}$ (60-110)
Glucose	4.0 mmol/L (4.0-7.8)

What is the most appropriate next step management step?

[Salbutamol nebuliser5%](#)[Broad-spectrum antibiotics5%](#)[Sliding scale insulin infusion4%](#)[Intravenous hydrocortisone81%](#)[Restart anti-retroviral medications5%](#)

Adrenal insufficiency affects approximately 10% of patients with HIV, commonly due to cytomegalovirus (CMV)-related necrotising adrenalitis. It is the failure of the adaptive immune system seen in HIV infection, and particularly AIDS, that increases susceptibility to CMV infection, and thus risk of CMV-associated adrenal failure.

The immediate management of hypoadrenalism involves rapid steroid replacement; fluid resuscitation would also be a priority.

There is no firm evidence here to suggest bacterial infection, and the hyperkalaemia should resolve with appropriate management of the hypoadrenalism.

## **Addisonian crisis**

### Causes

- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococemia)
- steroid withdrawal

### Management

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

### Question 3 of 54

A 53 year old gentleman attends his General Practitioner for a 'Well Man Check'. He has a past medical history of hypertension which has been treated with ramipril for 4 years. As part of the screening the GP

notes that the patient has been suffering from low back pain for the last couple of months. He has been taking paracetamol and ibuprofen that he has bought over the counter and this has eased his pain. His blood pressure today is 134/76 mmHg. His GP takes blood tests as part of the check and the results are shown below.

Hb 13.2 g/dl

Platelets  $312 \times 10^9/l$

WBC  $8.2 \times 10^9/l$

Na<sup>+</sup> 138 mmol/l

K<sup>+</sup> 6.6 mmol/l

Urea 6.2 mmol/l

Creatinine 114  $\mu\text{mol/l}$

His GP notifies the patient immediately on seeing these results and refers him to the local Medical Assessment Unit. Where more tests are carried out.

Arterial Blood Gases:

pH 7.34

PaCO<sub>2</sub> 5.1kPa

PaO<sub>2</sub> 12kPa

HCO<sub>3</sub><sup>-</sup> 20 mmol/l

Serum Chloride 120mmol/l

Urinalysis:

pH 4.8

Protein negative

Blood negative

Leukocytes negative



Glucose negative

What is the most likely diagnosis?

[Renal Tubular Acidosis type 17%](#)[Renal Tubular Acidosis type 210%](#)[Renal Tubular Acidosis type 34%](#)[Renal Tubular Acidosis type 464%](#)[NSAID induced nephropathy15%](#)

This patient has RTA type 4. This often occurs asymptotically as in this case. In this case it's aetiology is likely secondary to ibuprofen use which has caused an aldosterone resistance in the proximal tubule of the nephron. It is associated with a mild metabolic acidosis and classically presents in patients with a high serum potassium. Urinary pH is commonly normal, but given that the nephron has not lost its hydrogen ion buffering capacity there is scope for the urinary pH to become more acidic to buffer the metabolic acidosis. The serum chloride level is high in this patient, with hyperchloraemia being a cardinal feature of all sub-types of RTA. When calculated, the anion gap in RTA type 4 is normal.

In NSAID induced nephropathy the urinalysis would show white cells (leukocytes) and may even show proteinuria.

## **Renal tubular acidosis**

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete  $H^+$ ) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased  $\text{HCO}_3^-$  reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

#### Question 4 of 54

A 26-year-old woman presents to the emergency department with vomiting. Her boyfriend describes her as being very unwell last few days becoming increasingly drowsy and struggling to eat or drink. She is known to have type 1 diabetes and no other medical problems. Following investigations she is diagnosed with diabetic ketoacidosis and is started on fixed-rate insulin regime, aggressive protocol-driven fluid resuscitation and close monitoring. Four hours into her admission she has significantly improved but the nursing staff are concerned because her blood glucose levels are coming down quickly. Capillary glucose levels have gone from 28.8 mmol/l to 7.2 mmol/l now. She has not managed to have anything to eat yet due to nausea, nor had her regular insulin dose. She is currently having a two hourly normal saline infusion with 40mmol of KCl. What is the most appropriate action in regards to her blood glucose?

[Stop the fixed rate insulin0%Convert the fixed rate insulin to sliding scale insulin0%Encourage oral intake of food0%Start IV dextrose alongside normal saline50%Start IV dextrose and stop normal saline50%](#)

DKA in the acute setting fixed rate insulin should be continued even if BM levels are  $<14$ ; IV dextrose should be added instead

This is a common scenario in diabetic ketoacidosis (DKA). She is a patient who was responded quickly in terms of blood glucose to insulin, but is not well enough to stop the insulin infusion. Stopping IV insulin in DKA should occur only when it is clear that there has been a resolution of the hyperglycaemic crisis. Resolution can be considered when pH is improving to  $>7.3$ , blood ketones are reduced  $<0.6\text{mmol/l}$  and the patient is able to eat adequately. This patient has not yet started eating so therefore this is not an option. If the patient has started to eat then they should have their regular mealtime insulin alongside the fixed rate insulin, and then have the fixed rate stopped within a short time, roughly 30 minutes. If there is resolution biochemically and there is another reason for which the patient is unable to eat, such as nil by mouth for surgery, then the fixed rate insulin should be converted to a sliding scale.

For this patient the fixed rate insulin should not be stopped as they have not yet manage to eat. This commonly occurs in DKA due to nausea and patients are likely to start feeling better after their metabolic abnormalities have been corrected. Therefore encouraging them to eat is unlikely to be helpful.

In order to maintain blood glucose levels and avoid hypoglycaemia, IV dextrose should therefore be prescribed. It is important to still follow the fluid replacement as patients who have DKA are significantly at fluid loss. In addition, they need rapid replacement of potassium. Therefore maintaining two fluid infusions is ideal for this patient.

## Diabetic ketoacidosis

Diabetic ketoacidosis may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction

### Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

## Diagnostic criteria

### American Diabetes Association (2009)

#### Key points

- glucose  $> 13.8$  mmol/l
- pH  $< 7.30$
- serum bicarbonate  $< 18$  mmol/l
- anion gap  $> 10$
- ketonaemia

### Joint British Diabetes Societies (2013)

#### Key points

- glucose  $> 11$  mmol/l or known diabetes mellitus
- pH  $< 7.3$
- bicarbonate  $< 15$  mmol/l
- ketones  $> 3$  mmol/l or urine ketones ++ on dipstick

## Management

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is  $< 15$  mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia

### **JBDS example of fluid replacement regime for patient with a sSystolic BP on admission 90mmHg and over**

<b>Fluid</b>	<b>Volume</b>
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

### **JBDS potassium guidelines**

<b>Potassium level in first 24 hours (mmol/L)</b>	<b>Potassium replacement in mmol/L of infusion solution</b>
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

### **Complications of DKA and its treatment**

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema\*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

\* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

### Question 5 of 54

A 68-year-old Indian patient presents to the emergency department with facial tetany, muscle cramps and paraesthesia of her fingers and toes. This is her second admission with similar symptoms. Her past medical history includes diffuse cutaneous systemic sclerosis with gastrointestinal, cutaneous and pulmonary manifestations. She was also diagnosed with vitamin D deficiency two years ago and receives regular vitamin D supplements. Her blood tests are as follows:

Hb	124 g/l
WBC	$8.0 \times 10^9/l$
Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	4.3 mmol/l
Urea	6.5 mmol/l
Creatinine	90 $\mu$ mol/l
CRP	15 mg/l
Corrected calcium	1.68 mmol/l
Phosphate	1.4 mmol/l
Magnesium	0.28 mmol/l
PTH	2 pmol/L (normal range = 8.5-12)
Amylase	14 u/l

Her symptoms improve with intravenous calcium replacement and intravenous magnesium replacement, correcting both electrolytes to within normal range. What is the underlying cause for these metabolic disturbances in this patient?

[Hypomagnesaemia31%](#) [Primary hypoparathyroidism49%](#) [Insufficient vitamin D supplementation10%](#) [Chronic kidney failure6%](#) [Chronic pancreatitis4%](#)

This complex picture investigates the underlying cause of hypomagnesaemia and hypocalcaemia in a patient with significant GI disease. With regular vitamin D supplementation, it is unlikely this is the cause. Her renal function is also within normal range. Although her parathyroid hormone levels are low, the likely underlying cause is due to insufficient magnesium absorption due to GI systemic sclerosis, which results in reduces parathyroid hormone release. There is nothing in the history to suggest a primary hypoparathyroidism or chronic pancreatitis.

### Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of

hypocalcaemia in the majority of cases

#### Causes

- vitamin D deficiency (osteomalacia)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion

Acute pancreatitis may also cause hypocalcaemia. Contamination of blood samples with EDTA may also give falsely low calcium levels

#### Management

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

#### Question 6 of 54

A 22-year-old student comes to the Emergency department with a cough productive of rusty coloured sputum. She has been suffering from increased shortness of breath, night sweats and fevers for the past 48 hours. Current medication includes daily hydrocortisone for congenital adrenal hyperplasia and the combined oral contraceptive pill. Current bloods are shown below:

Hb 131 g/l Na<sup>+</sup> 134 mmol/l

Platelets 201 \* 10<sup>9</sup>/l K<sup>+</sup> 4.1 mmol/l

WBC 14.9 \* 10<sup>9</sup>/l Urea 7.0 mmol/l

Neuts 10.1 \* 10<sup>9</sup>/l Creatinine 82 µmol/l

Lymphs 1.2 \* 10<sup>9</sup>/l CRP 185 mg/l

Eosin  $0.4 \times 10^9/l$

Which of the following is the most appropriate way to manage her steroid hormone replacement?  
How should you manage her steroid replacement?

[Convert to 200mg hydrocortisone IV BD8%](#)  
[Increase the daily dose by 50%28%](#)  
[Increase the daily dose by 100%57%](#)  
[Reduce the daily dose by 50%4%](#)  
[Keep the daily dose the same4%](#)

Patients with congenital adrenal hyperplasia who are managed with steroid hormone replacement should be managed in the same way as patients with Addison's disease. In other words, during a period of significant acute infection like the pneumonia here, the dose of corticosteroid should be doubled.

With the patient able to swallow, having presented early with her pneumonia, switching to IV hydrocortisone would represent excess steroid replacement and is not appropriate here. The other options including only small increases in steroid dose, reductions or maintaining the status quo, run the risk of adrenal crisis.

## **Congenital adrenal hyperplasia**

### Overview

- group of autosomal recessive disorders
- affect adrenal steroid biosynthesis
- in response to resultant low cortisol levels the anterior pituitary secretes high levels of ACTH
- ACTH stimulates the production of adrenal androgens that may virilize a female infant

### Cause

- 21-hydroxylase deficiency (90%)
- 11-beta hydroxylase deficiency (5%)
- 17-hydroxylase deficiency (very rare)



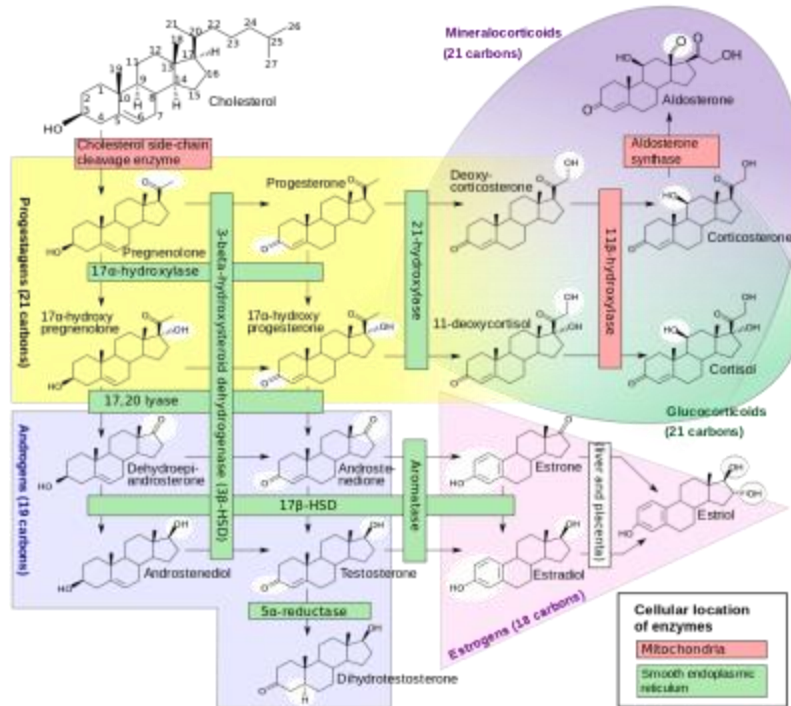


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/Steroid_hormone_synthesis)



### Question 1 of 48

A 66-year-old male was admitted with agitation and confusion, worsening over the past 1 week. His past medical history includes hypertension, ischaemic heart disease and chronic back pain. His daughter noticed that he had lost about 1 stone in weight (currently weighs 71 kg), has been more tired over the last month and that he has been drinking a lot more water. This was associated with the development of urinary incontinence.

On examination, his heart rate was 108 beats/min, blood pressure was 95/42 mmHg, saturations were 94% on air and respiratory rate was 20/min. He is confused, with a Glasgow Coma Scale of 14 and appeared dehydrated.

Blood results are as follows:

Na <sup>+</sup>	125 mmol/l
K <sup>+</sup>	5.0 mmol/l
Urea	18 mmol/l
Creatinine	180 $\mu$ mol/l
Blood glucose	34 mmol/l

Venous blood gas was done and showed the following:

pH 7.32  
pCO<sub>2</sub> 4.6 kPa  
pO<sub>2</sub> 6.1 kPa  
HCO<sub>3</sub> 17mmol/l  
BE -3.6 mmol/l

Which is the most important treatment?

Intravenous 0.9% sodium chloride 80% 10 units of human actrapid stat 4% Start insulin sliding scale at 6 units/hr 7% Calcium gluconate 4% Intravenous 1.8% sodium chloride 5%

Characteristic features of hyperosmolar hyperglycaemic state (HHS) includes:

- high osmolality, often 320 mosmol/kg or more
- high blood glucose, usually 30 mmol/L or more
- severely dehydrated and unwell.
- without significant hyperketonaemia or acidosis

HHS typically occurs in the elderly and is often the first presentation of Type 2 Diabetes Mellitus.

Using the blood results, osmolality can be calculated with the formula  $2(\text{Na} + \text{K}) + \text{glucose} + \text{urea}$

Goals of treatment include:

- Normalise the osmolality
- Replace fluid and electrolyte losses
- Normalise blood glucose
- Prevention of complications: Arterial or venous thrombosis/cerebral oedema

Fluid replacement must commence first; an initial insulin bolus of 0.15 U per kg may be given once infusions are underway. Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose. Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space, with a resulting decline in intravascular volume.

Patients with HHS are often exquisitely sensitive to insulin and require much lower doses than in diabetic ketoacidosis (DKA). The recommended insulin dose is a fixed rate intravenous insulin infusion (FRIII) given at 0.05 units per kg per hour (e.g. 4 units/hr in an 80 kg man) is used

Beware of rapid correction of hyponatraemia, may lead to cerebral pontine myelinolysis

Source: <http://www.diabetes.org.uk/Documents/Position%20statements/JBDS-IP-HHS-Adults.pdf>

## Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality  $>320 \text{ mosmol/kg}$
- Hyperglycaemia  $>30 \text{ mmol/L}$  with  $\text{pH} >7.3$ , bicarbonate  $>15 \text{ mmol/L}$  and no significant ketonuria  $<3 \text{ mmol/L}$

### Question 2 of 48

A 45-year-old woman comes to the clinic some 6 months after thyroid resection for differentiated thyroid cancer. She is well, has recovered from her surgery and has a neatly healed scar across her anterior neck. Blood pressure is normal at 110/80 mmHg, and her pulse is 60 and regular. Her body mass index is unchanged at  $25 \text{ kg/m}^2$ . Only medication is thyroid hormone replacement.

Which of the following is the most appropriate way to monitor for a recurrence?

[MRI neck 4%](#) [Technetium scanning 16%](#) [Thyroglobulin 62%](#) [Thyroid ultrasound scan 10%](#) [T3 levels 8%](#)

Given this patient is prescribed thyroid hormone replacement, monitoring of T3 or T4 is not useful in monitoring for cancer recurrence. On the other hand the presence of thyroglobulin does indicate thyroid gland activity which isn't suppressed by thyroid hormone replacement and is therefore potentially cancerous in origin. Levels should be undetectable.

Radiological investigations such as MRI neck, technetium scanning or thyroid ultrasound scanning are potentially less sensitive than monitoring for thyroglobulin and are therefore not a

preferred first line investigation. T3 levels are unsuitable as a marker of recurrence given that conversion of exogenously administered T4 to T3 confounds any measurement.

## Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

### Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

### Further information

Type	Notes
Papillary carcinoma	<ul style="list-style-type: none"><li>• Usually contain a mixture of papillary and colloidal filled follicles</li><li>• Histologically tumour has papillary projections and pale empty nuclei</li><li>• Seldom encapsulated</li><li>• Lymph node metastasis predominate</li><li>• Haematogenous metastasis rare</li></ul>
Follicular adenoma	<ul style="list-style-type: none"><li>• Usually present as a solitary thyroid nodule</li><li>• Malignancy can only be excluded on formal histological assessment</li></ul>
Follicular carcinoma	<ul style="list-style-type: none"><li>• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.</li><li>• Vascular invasion predominates</li></ul>

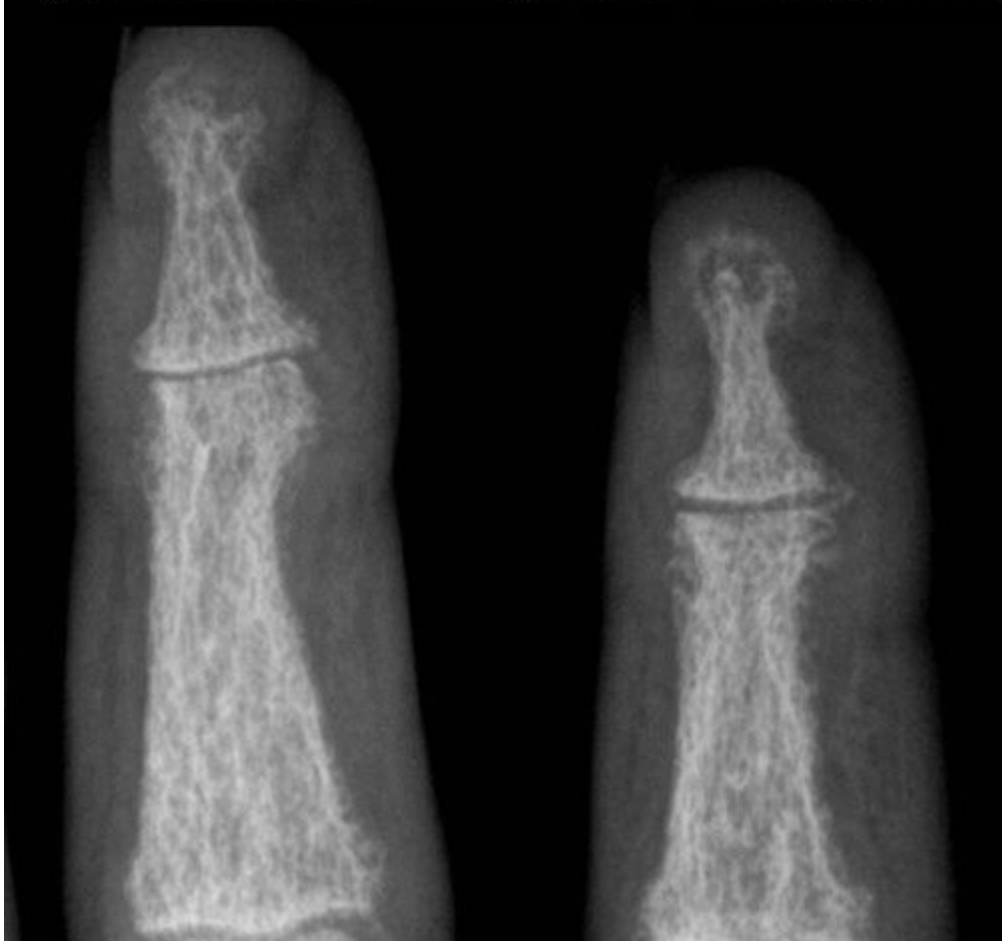
Type	Notes
Medullary carcinoma	<ul style="list-style-type: none"> <li>• Multifocal disease raree</li> <li>• C cells derived from neural crest and not thyroid tissue</li> <li>• Serum calcitonin levels often raised</li> <li>• Familial genetic disease accounts for up to 20% cases</li> <li>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.</li> </ul>
Anaplastic carcinoma	<ul style="list-style-type: none"> <li>• Most common in elderly females</li> <li>• Local invasion is a common feature</li> <li>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.</li> </ul>

#### Question 3 of 48

A 58-year-old woman of Indian ethnic origin presents with pain in her hands. These pains have been present for the past few months and are getting gradually worse. The hand pains are also associated with generalised aches which are worst around the shoulders, lower back and feet/ankles. On the review of systems she describes lethargy and polydipsia.

She has a past medical history of depression and hypertension which is well controlled with lisinopril.

A hand x-ray is requested:





What is the most likely underlying diagnosis?

[Osteomalacia23%Tuberculosis5%Hyperparathyroidism52%Psoriatic arthritis14%Osteoarthritis6%](#)

The x-rays demonstrate generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and sub-periosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with hyperparathyroidism.

Generalised aches and pain, polydipsia and lethargy are also common symptoms of having a raised calcium level.

## **Primary hyperparathyroidism**

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Features - 'bones, stones, abdominal groans and psychic moans'

- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture
- renal stones
- depression
- hypertension

### Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II

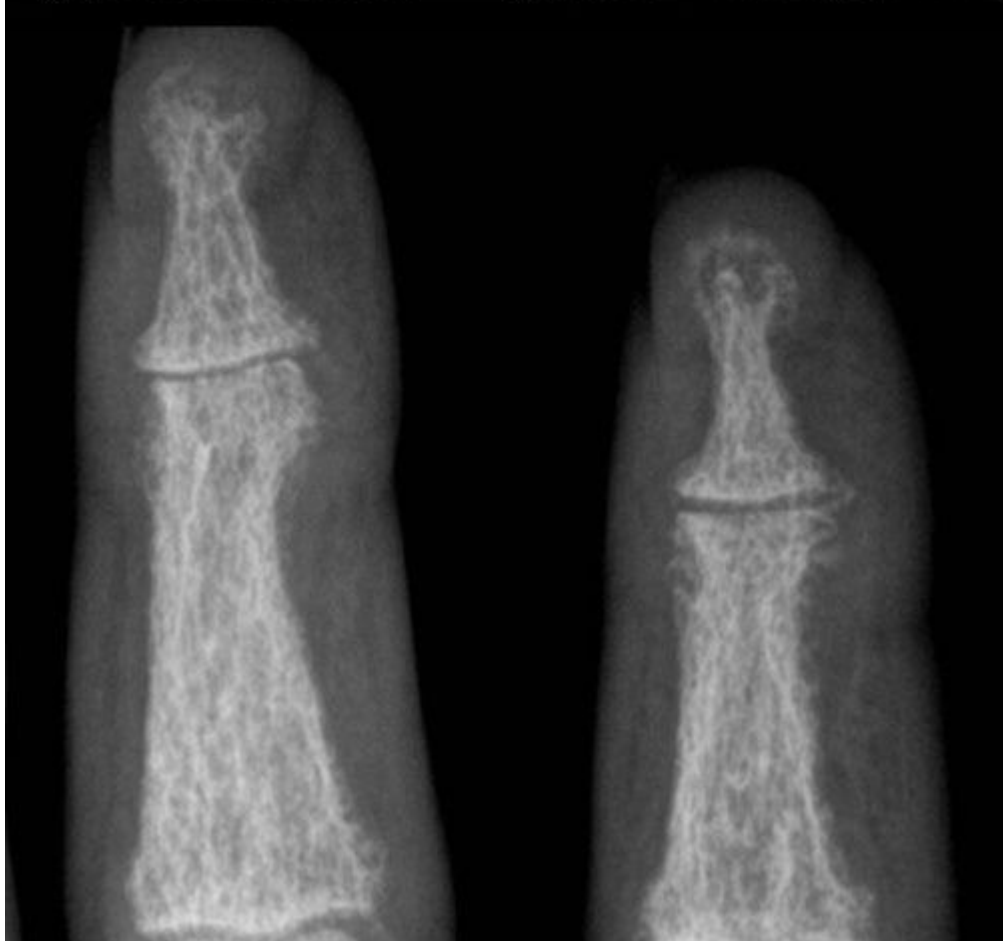
### Investigations

- raised calcium, low phosphate
- PTH may be raised or normal
- technetium-MIBI subtraction scan

### Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- calcimimetic agents such as cinacalcet are sometimes used in patients who are unsuitable for surgery







Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

#### Question 5 of 48

A 19 year-old woman presents for review. Her past medical history includes hypertension, which is managed with ramipril and indapamide and 11-beta hydroxylase deficiency, which was identified at birth upon identifying cliteromegaly.

Which of the following is likely to be raised most markedly?

[17-OH pregnenolone12%Oestradiol8%11-Deoxycortisol34%17-OH progesterone42%Oestrone4%](#)

11 Beta-hydroxylase is responsible for conversion of 11-deoxycorticosterone and 11-deoxycortisol to corticosterone and cortisol. In patients with 11-beta hydroxylase deficiency, this conversion does not occur in sufficient amounts and levels of these steroids accumulate in patient. Therefore, although 17-OH hormones may also be raised the 11-Deoxycortisol is the more significantly raised than the others.

## Congenital adrenal hyperplasia

### Overview

- group of autosomal recessive disorders
- affect adrenal steroid biosynthesis
- in response to resultant low cortisol levels the anterior pituitary secretes high levels of ACTH
- ACTH stimulates the production of adrenal androgens that may virilize a female infant

### Cause

- 21-hydroxylase deficiency (90%)
- 11-beta hydroxylase deficiency (5%)
- 17-hydroxylase deficiency (very rare)

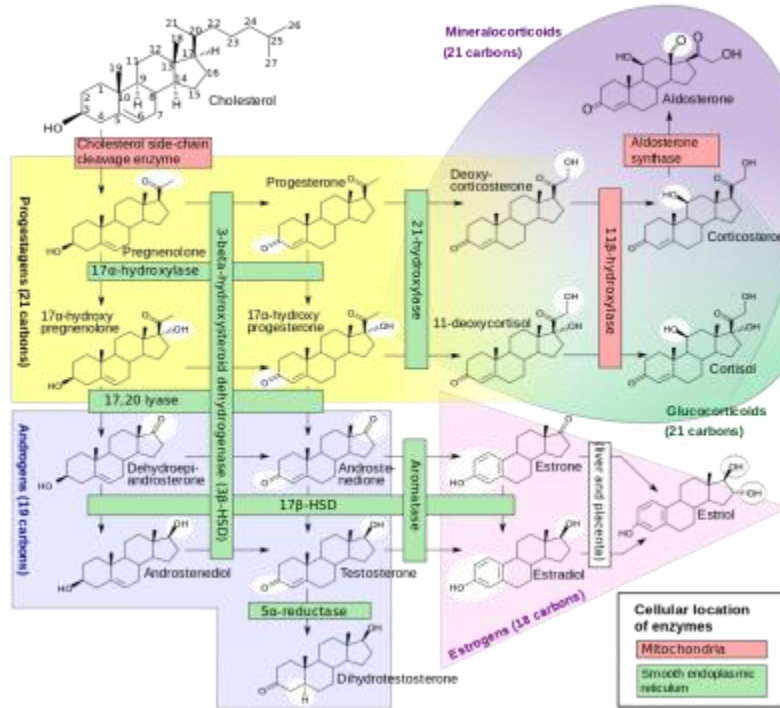


Image sourced from [Wikipedia](#)

### Question 1 of 42

A 28-year-old lady has noticed over the last year that she does not tolerate cold weather well. She is fatigued and her partner notices that she is also low in mood despite having no obvious triggers. Physical examination is unremarkable. Her electrocardiogram (ECG) demonstrates a sinus rhythm at 43 beats per minute. She has a background of type 1 diabetes mellitus for which she takes insulin. She also has coeliac disease. Her blood results are shown below:

Hb 136 g/l

MCV 103 fL

Na 133 mmol/l

K 4 mmol/l

Urea 3.5 mmol/l

Creatinine 70  $\mu$ mol/l

Glycosylated haemoglobin (HbA1c) 51 mmol/mol (6.8%)

TSH	9.2 mIU/L (reference range 0.3-4.0 mIU/L)
T3	2 pmol/L (reference range 3-9 pmol/L)
T4	5 pmol/L (reference range 9-25 pmol/L)

What is the next best step in her management?

[Commence levothyroxine51%](#)[Commence carbimazole3%](#)[Ultrasound scan thyroid7%](#)[MRI pituitary8%](#)[Short synacthen test31%](#)

Every time you see type 1 diabetes, pernicious anaemia, rheumatoid arthritis, coeliac, or indeed ANY of the autoimmune conditions in the past medical history of a patient in the exam engage autoimmune mode in your brain. Once you have done that, you will be specifically looking not to miss other coexistent autoimmune conditions they may be trying to hide from you behind a cryptic clinical sign or some subtle blood abnormality. In this example, where she has type 1 diabetes, thinking like that then gives you the diagnosis of an autoimmune hypothyroid cause (Hashimoto's). If you think you have made a diagnosis of Hashimoto's, you should routinely next always look to rule out Addison's, even if the sodium is normal (which it isn't in this example: a subtle blood abnormality). Addison's (just like other autoimmune conditions) may coexist with Hashimoto's. However, the danger of missing Addison's in Hashimoto's is that it sits there masked by the hypothyroid. If you miss it and treat the hypothyroid blindly first without covering the Addison's, you will unmask the Addison's and the patient will come back in an adrenal crisis a few days later.

### **Addison's disease: investigations**

In a patient with suspected Addison's disease the definite investigation is a ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If a ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:

- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia

- hyponatraemia
- hypoglycaemia
- metabolic acidosis

#### Question 2 of 42

A 62-year-old man with a diagnosis of Paget's disease is seen in clinic with a two month history of worsening bone pain, mainly in his left leg. His medications include paracetamol, ibuprofen, and alendronate.

Examination reveals marked deformity of the long bones, particularly the left tibia.

Blood tests:

Calcium 2.40 mmol/L (2.25-2.5)

Albumin 37g/L (34-54)

Corrected calcium 2.50 mmol/L (2.25-2.5)

Alkaline phosphatase 484 U/L (45-105)

Alanine transaminase 27 U/L (5-35)

What is the next stage in the treatment of this patient?

[Cholecalciferol13%](#)[Surgery14%](#)[Calcitonin57%](#)[Hearing aid5%](#)[Prednisolone12%](#)

Paget's disease is characterised by abnormal bone remodelling, particularly in the skull and long bones. The characteristic blood test results include an elevated alkaline phosphatase, with otherwise normal liver function tests (as alkaline phosphatase is also found in bone). A raised calcium may only be seen if there is associated immobility.

Analgesics and non-steroidal inflammatory drugs are initially used to manage pain, with treatment escalated to bisphosphonates and calcitonin in refractory cases.

#### Reference

Selby et al. Guidelines on the management of Paget's disease of bone. Bone,2002;31:36673.

## **Paget's disease of the bone**

Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

### Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

### Clinical features - only 5% of patients are symptomatic

- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium\* and phosphate are typically normal
- skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's

- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

### Complications

- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



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The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.

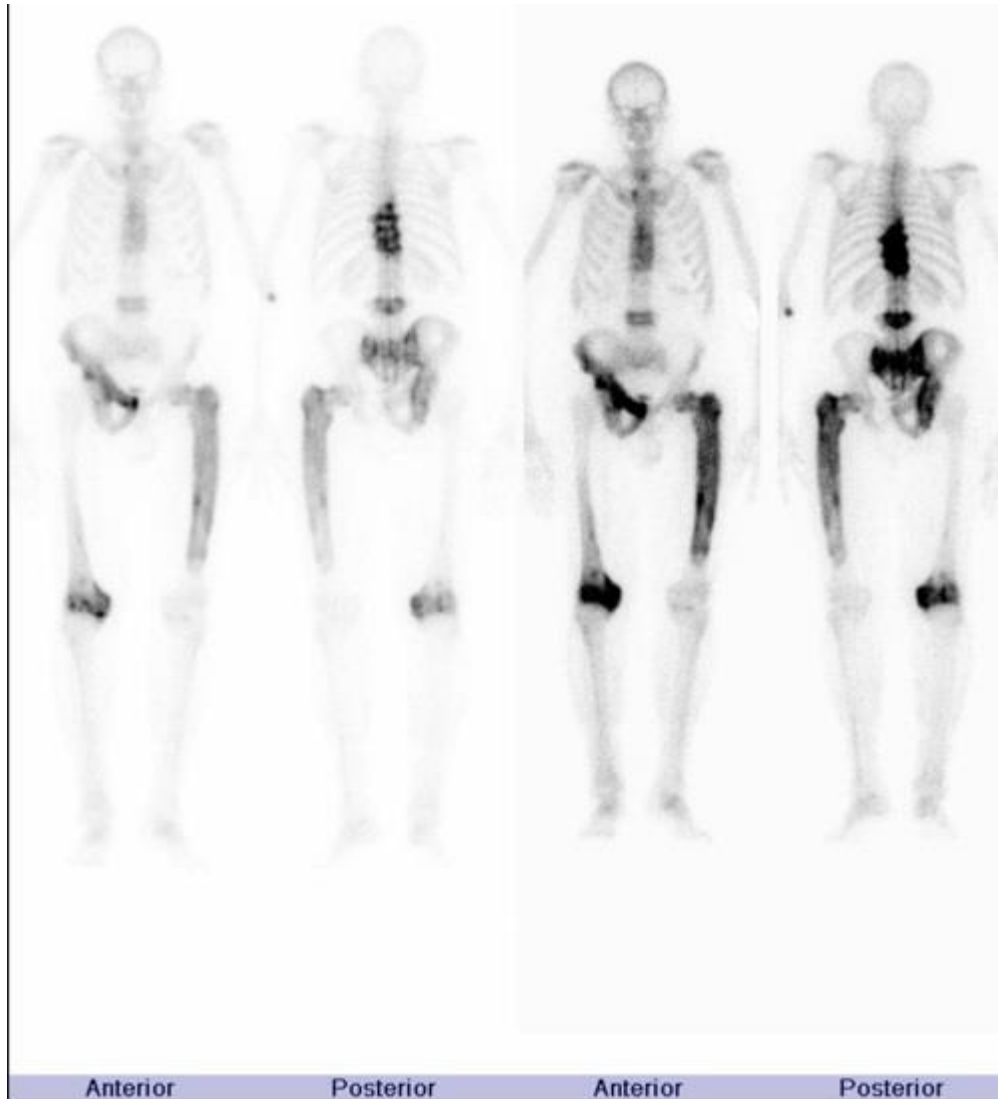


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Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.





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Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

### Question 3 of 42

A 24-year-old nurse presents after collapsing on a night shift. His blood glucose is measured at being 1.4 mmol/l. His blood pressure at the time was noted to be 115/82 mmHg. He has no palpitations and had not bitten his tongue or become incontinent during the episodes. He was shaken afterwards, although did not have memory loss and stated he had not tripped over anything. He also said he has had five of these episodes over the last two weeks.

Blood tests are sent off and unremarkable except for a low-normal C-peptide level and markedly raised insulin level.

Which of the following is the most likely diagnosis of his multiple episodes of collapse?

[Sulphonylurea misuse10%](#) [Insulin misuse72%](#) [Alcohol misuse3%](#) [Retroperitoneal sarcoma3%](#) [Insulinoma11%](#)

Hyperinsulinaemia in the absence of raised C-peptide points towards the diagnosis of insulin abuse. Elevation of C-peptide, when combined with hyperinsulinaemia suggests sulphonylurea abuse. To rule this out it may be appropriate to assay levels of commonly used sulphonylureas in urine. Insulinomas are a more rare cause of repeated hypoglycaemic episodes.

## Hypoglycaemia

### Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol

### Other possible causes in children

- nesidioblastosis - beta cell hyperplasia

#### Question 4 of 42

A 24 year old student nurse is brought to the Emergency Department having collapsed at work. Apart from depression for which she takes sertraline, she has no other past medical history. This is her third collapse in a month. On each attendance capillary blood glucose measurements have been  $< 4\text{mmol/L}$ . An oral glucose tolerance test performed two weeks previously by her GP was normal.

Today:

C-peptide  $3.9\text{ng/ml}$  ( $0.8 - 3.1\text{ng/ml}$ )

Glucose  $3.4\text{mmol/L}$

What is the most appropriate next investigation?

[Early morning C-peptide levels11% Toxicology screen13% CT scan of pancreas14% No further investigations, advise her to stop self-administering insulin22% 72 hour fast40%](#)

The key to this question is the recognition that C - peptide is increased by endogenous insulin and suppressed by exogenous insulin. Therefore it is likely that this patient has an excess of endogenous insulin ie. insulinoma.

The gold standard investigation for an insulinoma is the 72 hour fast during which C - peptide and insulin levels are measured. The tumour may be too small to be seen on CT and therefore endoscopic ultrasound is the preferable investigation if the diagnosis is still suspected despite a normal fast.

### **Insulinoma**

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

#### Basics

- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

#### Features

- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

## Diagnosis

- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

## Management

- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

## Question 8 of 42

A 38-year-old woman is referred to the outpatient department by her GP with pain in her calves when walking 50 meters. She reports no other symptoms and has no other past medical history other than migraine. She is on no regular medication and her family history includes her mother having diabetes and her father dying of a heart attack aged 46. She currently smokes 35 cigarettes per day and drinks a glass of wine every evening. Her occupation is as a financial advisor.

Examination reveals tendon xanthomas affecting the extensor tendons of his fingers. On examining her face it is noticed she has xanthelasma around both eyes and corneal arcs.

Which of the follow is the most likely diagnosis?

[Tangier disease](#)5% [Homozygous familial hypercholesterolaemia](#)24% [Heterozygous familial hypercholesterolaemia](#)49% [Familial hypertriglyceridaemia](#)17% [Apo CII deficiency](#)6%

This patient's symptoms suggest intermittent claudication and combined with the signs of hypercholesterolaemia especially the tendon xanthomas would suggest one of the familial hypercholesterolaemias. Patients with homozygous familial hypercholesterolaemia, present with early cardiovascular disease, sometimes as early as the second decade of life, whereas, patients with heterozygous familial hypercholesterolaemia rarely present before the age 30. Thus, this case is more suggestive of heterozygous familial hypercholesterolaemia.

In heterozygous familial hypercholesterolaemia, total cholesterol would typically be above 7.9 mmol/l, with normal triglyceride levels. In homozygotes it is typically above 15 mmol/l.

## **Familial hypercholesterolaemia**

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

## **Management**

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- the maximum dose of potent statins are usually required
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

## **Question 1 of 32**

A 20-year-old nurse with no past medical history presents following a collapse with a blood sugar 1.5 mmol/l. You phone her general practitioner and find out she has had 6 month history of episodes hypoglycemia. The cause has not been established and she is awaiting an outpatient

endocrinology opinion. In hospital her bloods come back showing an insulin level 350 mIU/L (18-276) 1 hour after lunch. Her C-peptide level at this time is 3.50 ng/ml (0.51 to 2.72). Her TSH is 0.03 mIU/L. What test should be performed next?

[Urgent MRI pancreas 26%](#) [Urgent ultrasound thyroid 4%](#) [Urgent MRI head 11%](#) [Urine or serum sulphonylurea levels 48%](#) [Short Synacthen test 10%](#)

Sulphonylureas increase the release of pro-insulin and hence give a similar biochemical picture to an insulinoma. The co-existing low TSH in a young female patient with access to hospital drugs raises the possibility of exogenous medication use. Testing the patient's urine or serum for sulphonylurea levels would be an easy, low cost and simple test prior to further work up. The levels would obviously be zero in a patient with an insulinoma. In patients illicitly taking exogenous insulin one would expect high insulin levels but low C-peptide levels.

## Hypoglycaemia

### Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol

### Other possible causes in children

- nesidioblastosis - beta cell hyperplasia

### Question 3 of 32

A 22-year-old woman with a history of partial Kallmann syndrome comes to the fertility clinic for review. She got married some 6 months earlier and wants to start a family. She has normal external genitalia and sparse pubic and axillary hair and has a normal body mass index of 23 kg/m<sup>2</sup>. Which of the following is the most appropriate intervention?

[Clomiphene 21%](#) [HCG and FSH then IVF 54%](#) [Metformin 5%](#) [Oestrogen 7%](#) [Referral for adoption 13%](#)

The correct answer is HCG and FSH then IVF. Restoration of ovulation in females with Kallmann syndrome is complex and often requires HCG to drive production of gonadal steroid hormones, FSH to drive ovulation, harvesting of eggs, and IVF. This process is most effective in achieving successful pregnancy.

Clomiphene does induce ovulation and is useful in patients with other conditions such as polycystic ovarian syndrome. It is however very unlikely to be effective in patients with gonadotrophin failure like Kallmann syndrome. Metformin has previously been used in the management of PCOS. Oestrogen doesn't restore ovulation in patients with Kallmann syndrome but may be considered for patients who don't want to get pregnant. In the event that fertility treatment isn't successful, adoption can be considered.

### **Kallman's syndrome**

Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

#### **Features**

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

#### **Question 1 of 27**

A 62-year-old woman attends her GP complaining of weight gain, lethargy and hair loss. She denies any intercurrent illness. Thyroid function tests are performed and the results are as follows:

Thyroid stimulating hormone (TSH) 0.3 mu/l  
Free T4 8 pmol/l

Which investigation is most likely to be diagnostic?

[Thyroid ultrasound9%](#)[Radio-iodine uptake scan18%](#)[Anti-thyroid peroxidase \(TPO\) antibodies28%](#)[Fine-needle aspiration of thyroid5%](#)[MRI pituitary gland40%](#)

This patient has hypothyroidism. The vast majority of cases are primary hypothyroidism with a high TSH and low T4. The common causes are:

- Autoimmune (Hashimoto's disease, atrophic)
- Iodine deficiency
- Thyroiditis (post-viral, post-partum)
- Iatrogenic (thyroidectomy, radioiodine, drugs)

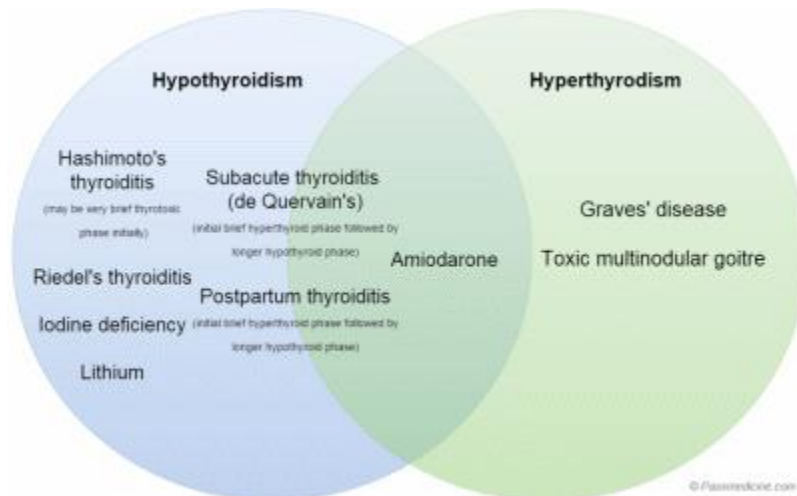
Secondary hypothyroidism is very rare and results in a low TSH and low T4. In these cases, pituitary insufficiency is most likely and therefore an MRI of the gland should be performed.

## Thyroid function tests

The interpretation of thyroid function tests is usually straightforward:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	In T3 thyrotoxicosis the free T4 will be normal
Primary hypothyroidism (primary atrophic hypothyroidism)	High	Low	
Secondary hypothyroidism	Low	Low	Replacement steroid therapy is required prior to thyroxine
Sick euthyroid syndrome*	Low**	Low	Common in hospital inpatients T3 is particularly low in these patients
Subclinical hypothyroidism	High	Normal	
Poor compliance with thyroxine	High	Normal	
Steroid therapy	Low	Normal	





Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

\*now referred to as non-thyroidal illness

\*\*TSH may be normal in some cases

## Question 2 of 27

A 68-year-old gentleman was admitted to the medical admissions unit with increasing drowsiness. He had been diagnosed with primary small cell carcinoma of the lung six months ago and had declined curative chemotherapy. At the time of diagnosis there was no evidence of metastasis, and his past medical history comprised of chronic obstructive pulmonary disease, ischaemic heart disease, hypertension, hypercholesterolaemia and depression.

His wife had taken him to the Emergency Department having noted that he had been increasingly drowsy over the last few hours, as well as developing new onset confusion. He had otherwise been relatively well prior to the admission. He had consulted his GP about new onset generalised aches and pains within the last four weeks for which his GP had commenced Oramorph solution PRN. Since then he had developed abdominal pain which the GP had diagnosed as secondary to opiate-induced constipation and he was accordingly prescribed lactulose 15ml BD with partial relief of his symptoms. There had been no evidence of weakness or numbness and no evidence of speech impairment; as far as his wife was aware he had taken the prescribed dose of oramorph. His drug history comprised of oramorph solution 10mg BD, paracetamol 1g QDS, dihydrocodeine 60mg QDS, lactulose 15ml BD, aspirin 75mg OD, atorvastatin 20mg ON, bisoprolol 2.5mg OD, Ramipril 2.5mg OD and furosemide 40mg OD.

Examination revealed a drowsy gentleman with a GCS of 12 (E 3 M5 V4). His blood pressure was 102/68, heart rate 58bpm, respiratory rate 10/min, oxygen saturations of 95% on air and temperature 36.6°C. Examination of his cardiovascular and respiratory systems were

unremarkable. Examination of his central nervous system revealed the presence of normal sized pupils; he was not compliant with formal neurological examination but no other focal neurological signs were found. There was no evidence of neck stiffness and Kernig's sign was negative. He was not cooperative with an abbreviated mental state examination.

Which investigation is most likely to be diagnostic of the underlying cause?

[Urgent CT head scan24%](#) [Urgent serum liver function and calcium profile56%](#) [Urgent isotope bone scan7%](#) [Urgent septic screen6%](#) [Urgent PET scan7%](#)

This gentleman has developed signs of life-threatening hypercalcaemia, having manifested previous potential symptoms including new onset abdominal pain and constipation. This question is asking what the single next most important investigation should be, and whilst most of the above options are relevant, candidates are asked to discriminate from what is deemed to be the next essential management should be. It is likely that he has developed metastasis to his spine thus whilst an isotope bone scan may be an important part of his overall management, it is not as relevant in the acute setting. Likewise, it is likely that a septic screen and CT head would be performed, but clinically speaking there is little definite evidence of acute raised intracranial pressure or sepsis. There is no indication at present that he is suffering from opiate toxicity and therefore IV naloxone should not be administered at this stage.

## **Hypercalcaemia: causes**

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to number of processes, including; bone metastases, myeloma, PTHrP from squamous cell lung cancer

Other causes include

- sarcoidosis\*
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs: thiazides, calcium containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone\*\*

\*other causes of granulomas may lead to hypercalcaemia e.g. Tuberculosis and histoplasmosis

\*\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilization

#### Question 4 of 27

A 62-year-old man comes to the Emergency department with nausea and vomiting which has steadily worsened over the past 2-3 weeks. He had Type 2 diabetes for the past 7 years and is currently treated with metformin, sitagliptin and empagliflozin. He tells you he has lost some 5kg in weight over the past month. On examination his blood pressure is 110/65 mmHg, his pulse is 85 beats per minute and regular. Emergency blood testing reveal elevated ketones and a glucose of 12.2 mmol/l.

Which of the following is the most appropriate way to manage his glucose control?

[Add liraglutide5%](#)[Add long-acting insulin16%](#)[Change the empagliflozin for liraglutide23%](#)[Change the empagliflozin for long-acting insulin42%](#)[Stop the metformin14%](#)

Given the duration of Type 2 diabetes and the fact that patient has lost weight in the past month, the possibility that he is insulinopenic is raised. In this situation, calorie loss and metabolic disturbance can be exacerbated by the use of SGLT-2 inhibitors and patients may present as here, with euglycaemic ketoacidosis. The SGLT-2 inhibitor should be withdrawn, and given he is insulinopaenic, long-acting insulin added.

In this situation the empagliflozin must be withdrawn, therefore options including adding liraglutide and long-acting insulin are incorrect. GLP-1 agonists such as liraglutide work less well in patients who are relatively insulinopenic, so liraglutide is incorrect. Stopping the metformin won't remove the cause of ketosis, the empagliflozin.

<http://care.diabetesjournals.org/content/38/9/1638>

#### Question 6 of 27

A 65-year-old gentleman presents with a 3 week history of general malaise, decreased oral intake and drowsiness. He has a past medical history of ischaemic heart disease, type 2 diabetes mellitus and gastritis. He lives alone with no carers and normally mobilises independently. A concerned neighbour went in to check on him after he was not seen for a few days. On examination his mouth is dry with reduced skin turgor. Heart sounds are normal, chest is clear, abdominal palpation reveals lower abdominal tenderness. ECG shows sinus tachycardia. Urine

dip shows ketones +, glucose +++.

Blood tests show:

Hb	140 g/l	Na <sup>+</sup>	150 mmol/l
Platelets	525 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.2 mmol/l
WBC	14 * 10 <sup>9</sup> /l	Urea	13 mmol/l
Neuts	10 * 10 <sup>9</sup> /l	Creatinine	160 µmol/l
Lymphs	2 * 10 <sup>9</sup> /l	CRP	56 mg/l
Eosin	0.5 * 10 <sup>9</sup> /l		

Venous blood gas shows no signs of acidosis. Formal blood glucose is phoned back as 40 mmol/L.

What is the most important initial treatment?

[Intravenous insulin4%](#)[Low molecular weight heparin4%](#)[Antibiotics3%](#)[Subcutaneous insulin3%](#)[Intravenous fluids87%](#)

The patient is clinically and biochemically dehydrated. Intravenous fluid resuscitation may be enough to normalise blood sugars. If hyperglycaemia is not responding then insulin may be required. Assessment for precipitant cause is also important such as infection, change in medicines, cardiovascular event etc. Low molecular weight heparin should be prescribed unless any contraindications due to the increased risk of venous thromboembolism associated with this condition.

## **Hyperosmolar hyperglycaemic state**

Hyperosmolar hyperglycaemic state (HHS) is confirmed by:

- Dehydration
- Osmolality >320mosmol/kg
- Hyperglycaemia >30 mmol/L with pH >7.3, bicarbonate >15mmol/L and no significant ketonenaemia <3mmol/L

### Question 7 of 27

You are asked to review a 55-year-old male surgical for the fourth time in seven days with persistent hyperkalaemia on his blood tests. He has been admitted for 5 weeks under the surgeons following AP resection of sigmoid carcinoma complicated by a superficial wound infection requiring a vacuum dressing. In all of the previous three medical reviews, the patient presented with a serum potassium of greater than 6.5 mmol/l and was treated with insulin-dextrose and calcium gluconate.

His past medical history includes type 2 diabetes mellitus, non-alcoholic steatohepatitis and neuromyelitis optica diagnosed 6 years ago and stable on the last review 2 months ago. His regular medications include gliclazide 80mg BD, Lantus (insulin glargine) 15 units OD, prednisolone 15 mg OD and baclofen 10mg QDS. During this review, he is alert and comfortable, blood pressure measures 135/82 mmHg, heart rate 90/min and sinus.

His blood tests are as follows:

Hb 121 g/l

Platelets  $334 \times 10^9/l$

WBC  $8.2 \times 10^9/l$

Na<sup>+</sup> 136 mmol/l

K<sup>+</sup> 6.9 mmol/l

Urea 7.5 mmol/l

Creatinine 110  $\mu\text{mol/l}$

CRP 4 mg/l

Renin Raised

Aldosterone Decreased

Blood gases show the following:

pH 7.24

PaO<sub>2</sub> (air) 15.8 kPa

PaCO<sub>2</sub> 2.2 kPa

Bicarbonate 24 mmol/l

Urinary pH = 6.2

A repeat CT abdomen and pelvis demonstrates appropriate wound healing with no local collections at the resection site. No other abdominal pathology is noted.

What is the most likely diagnosis?

[Type 1 renal tubular acidosis8%](#)[Type 2 renal tubular acidosis7%](#)[Type 4 renal tubular acidosis65%](#)[Waterhouse-Friderichsen syndrome10%](#)[Addisonian crisis10%](#)

Refractory hyperkalaemia in a patient with a prolonged illness should raise suspicions for adrenal insufficiency. Note that mineralocorticoid deficiency can occur with hyperkalaemia alone without hyponatraemia. In this case, the serum demonstrates a metabolic acidosis with normal bicarbonate and urinary pH greater than 5.5, ruling out type 1 and 2 renal tubular acidosis (RTA). Waterhouse-Friderichsen syndrome is caused by adrenal haemorrhage, classically secondary to tuberculosis or meningococcal infection, which if present, should be visualised on CT imaging. He does not demonstrate circulatory collapse, abdominal pain or nausea suggestive of Addisonian crisis. Type 4 RTA, causing a failure of the sodium-potassium antiporter is thus the most appropriate diagnosis, in the context of a patient with chronic steroid use and hence predisposition for adrenal insufficiency during acute severe illness.

## Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete H<sup>+</sup>) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased  $\text{HCO}_3^-$  reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

#### Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

#### Question 8 of 27

A 29-year-old woman is referred by her GP to the outpatient department with increasing symptoms of heat intolerance, diarrhoea and anxiety over the past couple of weeks. The patient is 34 weeks pregnant with her first baby and has a past medical history of hyperthyroidism, currently being treated with 10mg carbimazole. She has no other past medical history of note and her mother also had hyperthyroidism. She does not smoke or drink alcohol and does not take any recreational drugs.

On examination, her pulse is 98 beats per minute, blood pressure is 124/82 mmHg and her respiratory rate is 14/min. Her oxygen saturation is 98% and temperature is 37.5°C.

Blood tests are performed and reveal:

Thyroid stimulating hormone (TSH)	0.04 mu/l
Free thyroxine (T4)	21 pmol/l
Total thyroxine (T4)	152 nmol/l

What is the most appropriate management?

[Refer patient for immediate caesarean section9%Increase carbimazole dose to 20mg once daily48%Commence radioiodine treatment3%Switch carbimazole to propylthiouracil35%Refer for a thyroidectomy4%](#)

The carbimazole can be increased to up to 20mg once daily during pregnancy. Propylthiouracil can be started instead of the carbimazole if the increased carbimazole dose does not adequately control the patients hyperthyroidism.

#### Pregnancy: thyroid problems



In pregnancy there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level

## **Thyrotoxicosis**

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in second and third trimester

### **Management**

- propylthiouracil has traditionally been the antithyroid drug of choice. This approach was supported by the 2007 Endocrine Society consensus guidelines
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

## **Hypothyroidism**

### **Key points**

- thyroxine is safe during pregnancy
- serum thyroid stimulating hormone measured in each trimester and 6-8 weeks post-partum
- some women require an increased dose of thyroxine during pregnancy
- breast feeding is safe whilst on thyroxine

### **Question 9 of 27**

A 76-year-old man is taken to the Emergency Department from his nursing home after falling in his room. Since the fall he has been complaining of pain in the left hip and has been walking with a limp. His past medical history includes benign prostatic hyperplasia, Alzheimer's disease and hypertension.

An x-ray of his hip is requested:



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What is the most likely diagnosis?

[Hyperparathyroidism6%](#)[Osteomalacia9%](#)[Severe osteoarthritis of the left hip27%](#)[Paget's disease of the bone51%](#)[Metastatic prostate cancer7%](#)

The x-ray shows smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae. Paget's disease in the pelvis is often asymmetrical, for reasons that are not fully understood.

**Paget's disease of the bone**

Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients

#### Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium\* and phosphate are typically normal
- skull x-ray: thickened vault, osteoporosis circumscripta

Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's

- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

#### Complications

- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



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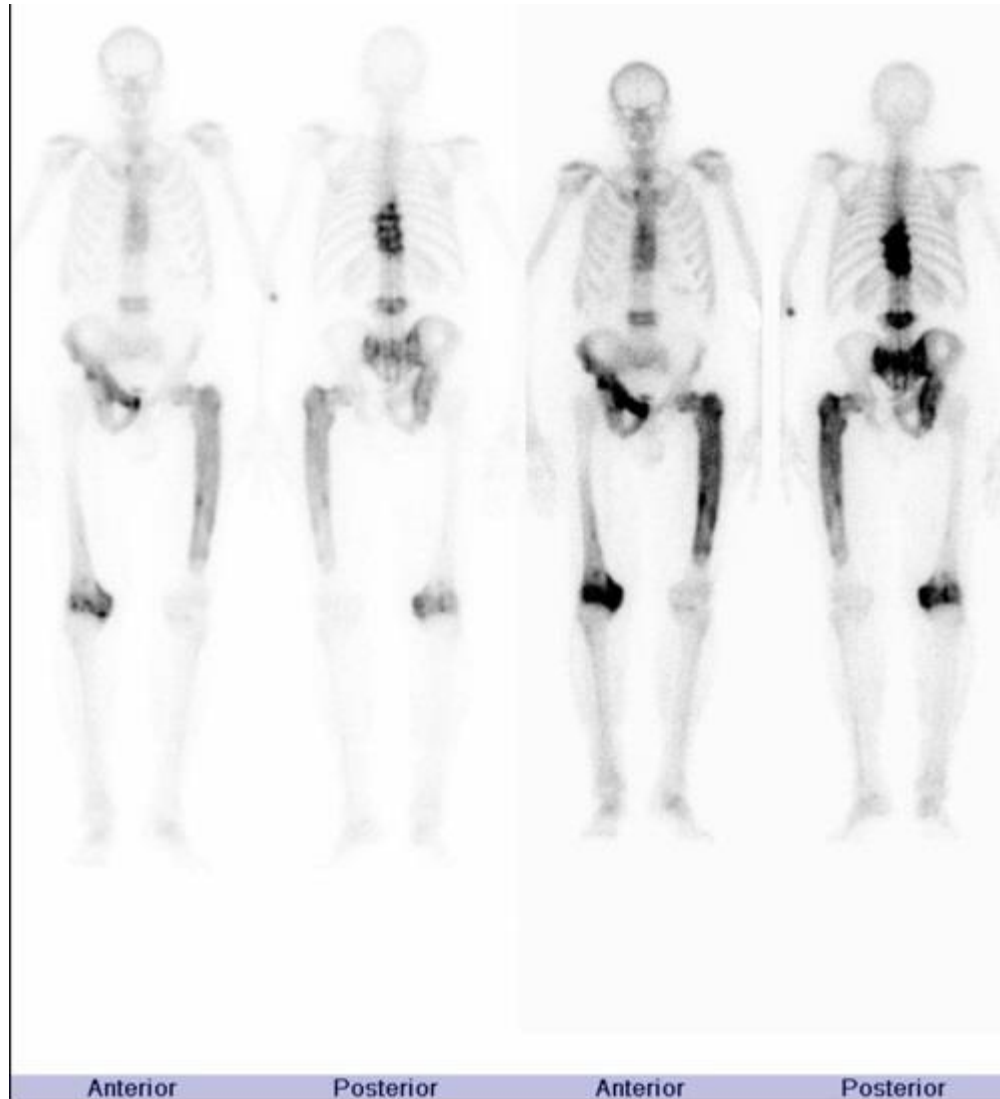
The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.



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Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.



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Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

\*usually normal in this condition but hypercalcaemia may occur with prolonged immobilization

### Question 1 of 17

A 37-year-old female presents to the medical outpatient department with a progressive loss of libido. She attributes this to persistent diarrhoea, which she has noted over the last 6 months. She has also lost 16kg of weight and feels fatigued. She has noticed that her eyes have become grossly protuberant and she has double vision on looking towards either the right or left. She also experiences painful watering of her eyes.

On examination she has a marked tremor in both hands, her heart rate is irregularly irregular and she has marked exophthalmos. There is an audible bruit on auscultation of the thyroid gland.

Her laboratory investigations reveal:

Hb 130 g/l  
MCV 77 fl  
MCH 29 pg  
WBC  $7.4 \times 10^9/l$   
Plt  $430 \times 10^9/l$   
TSH 0.03 mU/l (0.4–3.6 mU/l)  
Total T4 302 nmol/l (68–174 nmol/l)

CT scan of the orbits reveals taut optic nerves and retro-orbital oedema.

Which of the following would be the most appropriate management of her eye condition?

[Treatment with a block and replace regimen10%](#)[Treatment with radioactive iodine7%](#)[Treatment with IV methylprednisolone56%](#)[Surgical removal of the thyroid gland5%](#)[Orbital decompression surgery22%](#)

The question aims to address the ophthalmopathy associated with Graves disease and tests the candidates understanding of the correct approach to a patient with painful and significant eye disease. The treatment of choice is the administration of systemic steroids to lessen the inflammation and provide symptomatic relief. Treatment of the underlying thyrotoxicosis is essential, but it will not directly result in an improvement in the ophthalmopathy.

Radioactive iodine therapy may worsen Graves ophthalmopathy and should not be the initial treatment option. Treatment-induced hypothyroidism must be avoided as this may also worsen the eye problems.

### Thyroid eye disease

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

### Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

### Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

### Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

### Management

- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

### **Monitoring patients with established thyroid eye disease**

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes



- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

#### Question 2 of 17

A 72-year-old Japanese female presents to the emergency department with sudden onset shortness of breath associated with palpitations. She has previously experienced similar palpitations 6 months ago but did not seek medical attention. She was last completely well and described by her daughter to be at baseline 24 hours ago when they had dinner together. The patient denies any chest pain, nausea, vomiting or sweating. On examination, the patient is pyrexia at 38.2 degrees and tachycardic, with a regular pulse at 130-140 beats per minute. Heart sounds demonstrate a gallop rhythm; auscultation of her chest reveals bibasal inspiratory coarse crackles and no wheeze. She has bilateral mild lower limb pitting oedema to low ankles. Examination of the abdominal and neurological systems is unremarkable. A chest radiograph demonstrates bibasal alveolar shadowing with mild bilateral pleural effusions. An ECG demonstrates sinus tachycardia at 130 beats per minute. Blood tests are as follows:

Hb 123 g/l

Platelets  $299 \times 10^9/l$

WBC  $9.5 \times 10^9/l$

Na<sup>+</sup> 139 mmol/l

K<sup>+</sup> 4.2 mmol/l

Urea 7.2 mmol/l

Creatinine 98 µmol/l

TSH < 0.01 mU/l

Free T4 140 pmol/l

Free T3 40 pmol/l

Nursing staff have kindly taken blood cultures and taken measures to cool the patient. What is the next most appropriate immediate treatment?

[Intravenous propranolol 57% Lugol's iodine 18% Oral carbimazole 9% Oral propylthiouracil 6% Oral prednisolone 11%](#)

The patient has presented with sudden onset heart failure associated with sinus tachycardia, pyrexia and thyrotoxicosis: this represents a thyroid storm and is an endocrinological emergency. The treatment comprises of four aims: resuscitation, treat the sympathetic consequences of

thyrotoxicosis, block underlying hyperthyroidism and treat any heart failure present. The first step involved intravenous followed by oral beta-blockade. Diltiazem is an appropriate alternative if the patient cannot tolerate beta blockers. In cases of simultaneous poor ventricular function and thyroid storm, intravenous infusions of short-acting beta blockers such as esmolol are also appropriate, which can be switched off immediately at the earliest sign of worsening cardiac function secondary to beta blockade. Thyroid blockers can be instituted after this immediate therapy. Oral corticosteroids are also important to reduce peripheral T4 to T3 conversion. However, both treatments can be instituted after achieving haemodynamic stability.

## **Thyroid storm**

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm

Clinical features include:

- fever > 38.5°C
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test

## **Management**

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

A 60-year-old female presented with a six month history of polyuria, polydipsia and generalised aches and pains.

She is a known hypertensive for ten years and is taking bendroflumethiazide 2.5 mg daily. She has been taking calcium and vitamin D supplements for the last two years as she has a strong family history of osteoporosis.

On examination, her pulse rate is 80 beats per minute and her blood pressure is 150/90 mmHg. Cardiovascular, respiratory and abdominal examination were normal.

Investigations reveal:

Serum sodium	130 mmol/L
Serum potassium	3.1 mmol/L
Serum urea	7.7 mmol/L
Serum creatinine	88 mol/L
Serum corrected calcium	2.9 mmol/L
Phosphate	0.8 mmol/L
PTH	4.5 pmol/L (0.9-5.4)
Urinalysis	glycosuria ++

What is the most likely cause of this lady's symptoms?

[Primary hyperparathyroidism38%Vitamin D excess12%Bendroflumethiazide induced hypercalcaemia27%Familial hypocalciuric hypercalcaemia13%Diabetes mellitus9%](#)

This lady has hypercalcaemia which may be due to bendroflumethiazide or vitamin D excess, but the PTH level is inappropriately normal in the context of hypercalcaemia which indicates primary hyperparathyroidism rather than any other cause of hypercalcaemia in which the PTH would be suppressed by homeostatic mechanisms.

In addition, the phosphate level is low which is typical of primary hyperparathyroidism. The glycosuria is a distractor.

## Primary hyperparathyroidism

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

### Causes of primary hyperparathyroidism

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

### Features - 'bones, stones, abdominal groans and psychic moans'

- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture
- renal stones
- depression
- hypertension

### Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II

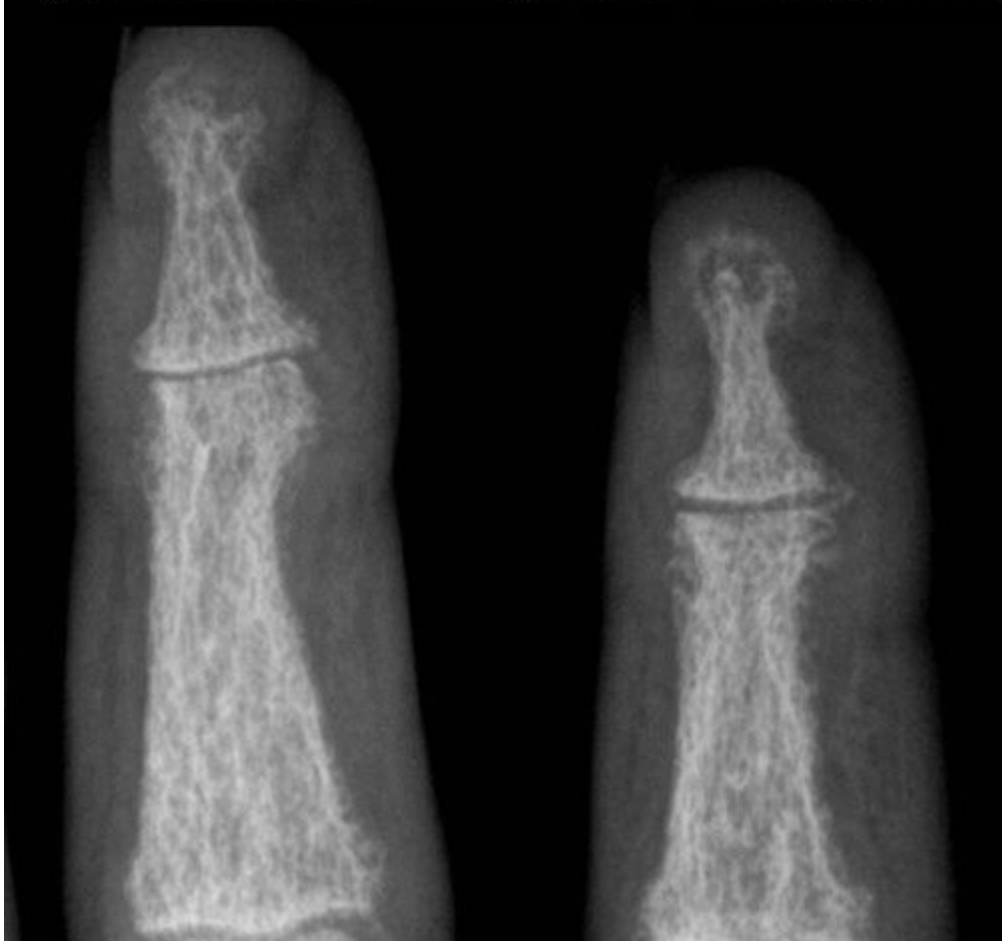
### Investigations

- raised calcium, low phosphate
- PTH may be raised or normal
- technetium-MIBI subtraction scan

### Treatment

- the definitive management is total parathyroidectomy

- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- calcimimetic agents such as cinacalcet are sometimes used in patients who are unsuitable for surgery





Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

### Question 3 of 17

A 60-year-old man attends a medical health check-up at his GP surgery. He was fit and well with a past medical history of childhood asthma and osteoarthritis in his fingers. His observations were included a blood pressure of 129/80 mmHg, pulse of 82 bpm, and oxygen sats of 97%.

Blood tests were performed and revealed:

Hb	138 g/l
Platelets	$190 \times 10^9/l$
WBC	$7.6 \times 10^9/l$
Na <sup>+</sup>	139 mmol/l
K <sup>+</sup>	3.9 mmol/l
Urea	4.1 mmol/l
Creatinine	9.2 $\mu$ mol/l
Bilirubin	15 $\mu$ mol/l
ALP	52 u/l
ALT	26 u/l
$\gamma$ GT	58 u/l
Albumin	40 g/l
Serum corrected calcium	2.77 mmol/L
Serum phosphate	0.90 mmol/l
Parathyroid hormone	5.9 pmol/L    normal range 1.2-5.8 pmol/L

A 24 hour urinary calcium test was performed based on the results above and revealed a result of 0.5 mmol/24 hours (normal range 2.4-7.4 mmol/24 hours)

What is the most likely diagnosis?

[Primary hyperparathyroidism24%](#)[Secondary hyperparathyroidism5%](#)[Vitamin D toxicity5%](#)[Multiple endocrine neoplasia type A3%](#)[Familial benign hypocalciuric hypercalcaemia63%](#)

Patients with familial benign hypocalciuric hypercalcaemia may have a normal or raised PTH. The most likely diagnosis in this scenario is familial benign hypocalciuric hypercalcaemia. Most cases are asymptomatic and blood test reveals hypercalcaemia with a reduced calcium urinary excretion rate (of under 0.02 mmol/L). There may also be normal to high parathyroid hormone, despite the elevated serum calcium levels.

### **Familial benign hypocalciuric hypercalcaemia**

Familial benign hypocalciuric hypercalcaemia is a rare autosomal dominant disorder characterised by asymptomatic hypercalcaemia. It is due to a defect in the calcium-sensing receptor and a decreased sensitivity to increases in extracellular calcium.

The parathyroid hormone level is often not suppressed, as would be expected in all non-hyperparathyroidism related cases of hypercalcaemia. This is due to the decreased sensitivity to increases in extracellular calcium.

#### **Question 5 of 17**

A 51-year-old lady librarian attends outpatient clinic with painful eyes. She reports that her vision has deteriorated over the past four weeks. On examination, she has proptosis, periorbital oedema and a painful complex ophthalmoplegia. She appears anxious and is worried about not coping at work. At present she smokes ten cigarettes daily.

What would be the most appropriate next step in managing this patient?

[IV methylprednisolone42%](#)[Surgical decompression9%](#)[Smoking cessation advice37%](#)[Total thyroidectomy7%](#)[Artificial tear drops5%](#)

IV methylprednisolone is the treatment of choice for moderately severe active Graves' ophthalmopathy. IV steroids have fewer side effects than oral steroids. If symptoms or vision do not improve then urgent surgical decompression should be considered.

Artificial tear drops are useful for symptomatic relief.

Total thyroidectomy has shown no benefit in the treatment of thyroid eye disease.



Outcomes have been shown to be worse in those patients who smoke, therefore smoking cessation advice should be given.

## **Thyroid eye disease**

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

### Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

### Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
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### Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

### Management

- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

## Monitoring patients with established thyroid eye disease

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

### Question 6 of 17

A 56-year-old man is referred to clinic by his General Practitioner as his GP had performed some routine blood tests which showed a K<sup>+</sup> of 2.8 mmol/l. The patient feels well in himself. His past medical history includes angina and renal stones. On examination his chest is clear and his abdomen is soft and non-tender.

Observations are as follows: temperature 36.3, blood pressure 132/86 mmHg, heart rate 78/min, respiratory rate 16/min, saturations 95% on air

His ECG shows normal sinus rhythm.

Investigations are as follows:

Na<sup>+</sup> 142 mmol/l

K<sup>+</sup> 2.8 mmol/l

Creat 117 µmol/l

Urea 9.6 mmol/l

Urinary K<sup>+</sup> 26 mmol/l (normal <20)

PaO<sub>2</sub> 11.2 kPa

PaCO<sub>2</sub> 3.6 kPa

pH 7.32

HC03- 18 mmol/l

Base excess -3 mmol/l

What is the most likely cause of his hypokalaemia?

[Barter's Syndrome 11%](#)[Liddle's Syndrome 8%](#)[Renal tubular acidosis type 1 59%](#)[Renal tubular acidosis type 2 14%](#)[Renal tubular acidosis type 4 9%](#)

All of these diagnoses could cause hypokalaemia except renal tubular acidosis type 4 which causes a hyperkalaemia.

When faced with a patient with hypokalaemia first check the urinary K<sup>+</sup>, if this is low you should consider gastrointestinal losses such as diarrhoea or vomiting or decreased intake of K<sup>+</sup>. If the urinary K<sup>+</sup> is high check the blood pressure, which in this case is normal. Liddle's Syndrome would cause hypertension.

If the patient is not hypertensive check the bicarbonate if it is low such as in this case the diagnosis is renal tubular acidosis. The clue here is that the patient has a history of renal stones meaning that the diagnosis is renal tubular acidosis type 1.

Renal tubular acidosis type 2 is associated with conditions such as Wilson's disease, lead poisoning and myeloma.

## Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal)

- inability to generate acid urine (secrete H<sup>+</sup>) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones

- causes include idiopathic, RA, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased  $\text{HCO}_3^-$  reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines

#### Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

#### Question 7 of 17

A 32-year-old man is reviewed in the ischaemic heart disease clinic having suffered an inferior myocardial infarction. He has been diagnosed with heterozygous familial hypercholesterolaemia and started on 80mg per day of atorvastatin. His LDL cholesterol is still 3.5 mmol/l.

Which of the following is the most appropriate next intervention?

[Add cholestyramine7%](#)[Add evolocumab28%](#)[Add fenofibrate36%](#)[Add nicotinic acid16%](#)[Change atorvastatin to rosuvastatin14%](#)

Although the 80mg of atorvastatin has clearly brought the LDL cholesterol much closer to target, but LDL of 3.5 mmol/l is still suboptimal given the history of an inferior myocardial infarction. Evolocumab, a PCSK9 inhibitor which interferes with degradation of the LDL receptor is the most appropriate intervention and can reduce LDL by a further 50%. Given his relatively young age and high lifetime risk of cardiovascular disease, he is exactly the type of patient likely to benefit from PCSK9 inhibition.

Cholestyramine was formerly used in the treatment of hypercholesterolaemia, it is a cholesterol binding resin, but is less effective in lowering cholesterol than a statin. Both fenofibrate and nicotinic acid have most effect in lowering triglycerides, and changing atorvastatin to rosuvastatin is likely to have limited benefit in further lowering LDL.

<https://www.medicines.org.uk/emc/medicine/30627>

#### **Familial hypercholesterolaemia**

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes

the LDL-receptor protein.

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

### Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- the maximum dose of potent statins are usually required
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

### Question 8 of 17

A 55 year-old female presents to the outpatients department having been referred by her GP. She complains of fatigue, increased sweating and weight loss over the past four months. She also reports a loss of sex drive.

Examination reveals that she is pale and has a pulse rate of 121 per minute with a bounding pulse character. Her blood pressure is 118/79 mmHg and she has heart sounds 1 and 2 presents with no added sounds. On auscultation, her chest is clear and her abdomen is soft and non-tender with no organomegaly. She has a smooth goitre but has no signs of thyroid eye disease. Examination of her cranial nerves are normal.

The results of recent blood tests are as follows:

Hb	11.3 g/dl
Platelets	$190 \times 10^9/l$
WBC	$10.9 \times 10^9/l$

Na<sup>+</sup> 129 mmol/l  
 K<sup>+</sup> 4.3 mmol/l  
 Urea 7.9 mmol/l  
 Creatinine 94 µmol/l  
 ALP 155 u/l  
 Calcium 2.40 mmol/l  
 Albumin 40 g/L  
 TSH 11 mU/L  
 Free T4 41 pmol/L  
 Free T3 11 pmol/L

Which of the following is the most likely diagnosis?

[Grave's disease13%](#)
[Thyroid cancer6%](#)
[Surreptitious thyroxine ingestion14%](#)
[De Quervain's thyroiditis8%](#)
[TSH secreting pituitary tumour59%](#)

Biochemistry reveals elevated thyroid-stimulating hormone (TSH) with concurrent elevated thyroxine (T4) and tri-iodothyronine (T3). An elevated alkaline phosphatase (ALP) is consistent with thyrotoxicosis. Hyponatraemia suggests hypoadrenalism.

Taken with the symptoms, this patient has a likely diagnosis of a thyrotropinoma, which is a rare type of pituitary tumour accounting for approximately less than 1% of cases of pituitary tumours. 90% are macroadenomas.

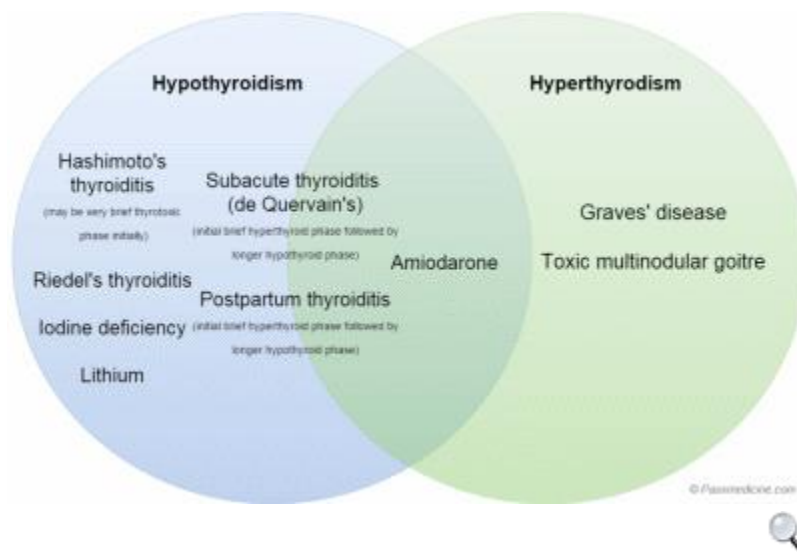
Presentation is typically with features of thyrotoxicosis and include weight loss, sweating, fatigue and tachycardia. There may also be signs of hypopituitarism.

## Thyroid function tests

The interpretation of thyroid function tests is usually straightforward:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	In T3 thyrotoxicosis the free T4 will be normal
Primary hypothyroidism (primary atrophic hypothyroidism)	High	Low	
Secondary hypothyroidism	Low	Low	Replacement steroid therapy is

Diagnosis	TSH	Free T4	Notes
Sick euthyroid syndrome*	Low**	Low	required prior to thyroxine Common in hospital inpatients T3 is particularly low in these patients
Subclinical hypothyroidism	High	Normal	
Poor compliance with thyroxine	High	Normal	
Steroid therapy	Low	Normal	



Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

\*now referred to as non-thyroidal illness

\*\*TSH may be normal in some cases

#### Question 9 of 17

An 18-year-old man comes to the endocrinology clinic for review. He has been transferred from the paediatric clinic with a diagnosis of congenital hypoparathyroidism and is treated with vitamin D and calcium supplementation. He has had one episode of symptomatic renal stones over the past 3 years and his creatinine is elevated at 125 micromol/l.

Which of the following is the most appropriate target with respect to serum calcium?

[1.85 mmol/16%](#) [2.10 mmol/141%](#) [2.25 mmol/139%](#) [2.60 mmol/110%](#) [2.85 mmol/14%](#)

This 18-year-old man is at risk of symptomatic hypocalcaemia because of congenital hypothyroidism, although elevating his calcium too much with vitamin D supplementation runs



the risk of symptomatic renal stones. As such guidelines recommend aiming towards a calcium just below the lower end of the normal range and 2.10 is an appropriate target for serum calcium.

1.85 mmol/l is considered too low and puts the patient at risk of muscle weakness, paresthesias, tetany and cardiac arrhythmia. Maintenance of calcium either at the upper end of the normal range, (2.60 mmol/l), or 2.85 mmol/l (above the normal range), is associated with symptomatic renal stones and progressive deterioration in renal function.

The European Endocrine Society Guidelines support this calcium target: (page G2)  
<http://www.eje-online.org/content/173/2/G1.full.pdf>

## **Hypoparathyroidism**

### **Primary hypoparathyroidism**

- decrease PTH secretion
- e.g. secondary to thyroid surgery\*
- low calcium, high phosphate
- treated with alfacalcidol

The main symptoms of hypoparathyroidism are secondary to hypocalcaemia:

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- Trousseau's sign: carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- Chvostek's sign: tapping over parotid causes facial muscles to twitch
- if chronic: depression, cataracts
- ECG: prolonged QT interval

### **Pseudohypoparathyroidism**

- target cells being insensitive to PTH
- due to abnormality in a G protein
- associated with low IQ, short stature, shortened 4th and 5th metacarpals
- low calcium, high phosphate, high PTH

- diagnosis is made by measuring urinary cAMP and phosphate levels following an infusion of PTH. In hypoparathyroidism this will cause an increase in both cAMP and phosphate levels. In pseudohypoparathyroidism type I neither cAMP nor phosphate levels are increased whilst in pseudohypoparathyroidism type II only cAMP rises.

#### Pseudopseudohypoparathyroidism

- similar phenotype to pseudohypoparathyroidism but normal biochemistry

\*this may seem an oxymoron, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism'

#### Question 10 of 17

A 23-year-old man is diagnosed as having type 1 diabetes mellitus after presenting with diabetic ketoacidosis. His blood sugars are now stable and he is well. What is the first-line insulin regime he should be offered?

[Twice-daily mixed insulin20%Once-daily mixed insulin3%Basal–bolus insulin regimen with twice-daily insulin detemir22%Basal–bolus insulin regimen with once-daily insulin glargine47%Rapid-acting insulin analogue before each meal with no longer acting insulin9%](#)

In newly diagnosed adults with type 1 diabetes, the first-line insulin regime should be a basal–bolus using twice-daily insulin detemir

### Diabetes mellitus: management of type 1

The long-term management of type 1 diabetics is an important and complex process requiring the input of many different clinical specialties and members of the healthcare team. A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

NICE released guidelines on the diagnosis and management of type 1 diabetes in 2015. We've only highlighted a very select amount of the guidance here which will be useful for any clinician looking after a patient with type 1 diabetes.

## HbA1c

- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

## Self-monitoring of blood glucose

- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

## Blood glucose targets

- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

## Type of insulin

- offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

## Metformin

- NICE recommend considering adding metformin if the BMI  $\geq 25$  kg/m<sup>2</sup>

A 22 year old lady presents over a year with mild-moderate, intermittent abdominal pain. She has felt low in mood over this period and also her periods have stopped. Her history includes two previous attacks of renal calculi formation managed conservatively. She had a car crash recently, where she says that the car just 'came out of nowhere'. She is intermittently getting global headaches that can be very severe in nature but are otherwise featureless. On prompting, she tells you that she has sometimes noticed a white nipple discharge on her clothing. She has had low blood pressure and several faints over this last year and after her GP discovered a low serum cortisol level he has started her on oral hydrocortisone and referred her to your clinic. On examination today her blood pressure 130/80. She has a blistering, red rash across her lower abdomen and back. Her abdomen is largely non-tender with no palpable organomegally or peritonism. Visual fields are reduced bitemporally. Her urine dipstick shows glycosuria. The remainder of the examination is unremarkable. Which of the following is likely to treat the underlying condition most effectively?

[Bisphosphonates 3% Surgery 61% Cabergoline 21% Octreotide 11% Insulin 3%](#)

The unifying diagnosis here is multiple endocrine neoplasia (MEN) type 1. MEN1 consists of tumours of the parathyroid, pituitary, and pancreas.

This patient has symptoms of hypercalcaemia (abdominal groans, renal stones, and psychic moans of the 'bones, stones, groans, psychic moans'). This can be caused by a parathyroid tumour. She has symptoms suggestive of a non-functioning pituitary macro-adenoma causing hyperprolactinemia (amenorrhea and galactorrhoea) and hypopituitarism presenting as Addison's from suppressed ACTH. Dopamine is the inhibitor of prolactin in the pituitary, and comes from the hypothalamus. A nonfunctioning pituitary macro-adenoma compresses the pituitary stalk, interrupting dopamine flow to the pituitary, and therefore abolishing dopaminergic inhibition of prolactin, resulting in hyperprolactinaemia. At the same time, the macro-adenoma causes hypopituitarism through local pressure effects on the pituitary itself. 76% of pituitary tumours in MEN1 are prolactinomas, with the remainder being nonfunctioning adenomas. Prolactinomas are extremely sensitive to medical management with e.g. cabergoline or bromocriptine and even shrink in size subsequently. First line treatment for nonfunctioning adenomas however is surgical removal. The glycosuria is suggestive of hyperglycaemia, which in the context of this MEN picture suggests a glucagonoma.

The answers try and trick you into looking to manage just one of the abnormalities here in an isolated fashion, e.g. targeting the pituitary with cabergoline, the pancreas with insulin, or the parathyroid with bisphosphonates. This may happen if you do not recognise that this is MEN. However, as the question asks what treatment is likely to treat the underlying condition, clearly insulin alone, cabergoline alone, or bisphosphonate alone will not suffice. Of the options available, only surgery can tackle all of the problems, and indeed is what most patients with MEN end up needing.

MEN is an autosomal dominant condition. MEN1 consists of tumours of the parathyroid, anterior pituitary, and pancreas:

- The parathyroid tumours cause hypercalcaemia and its symptoms (which don't forget include polyuria and polydipsia). The management of hypercalcaemia is fluid resuscitation and bisphosphonates.
- Pituitary tumours can be a prolactinoma, somatotroph adenoma (causing acromegally by secreting growth hormone), or an ACTH-secreting tumour causing Cushing's disease. There can be any combination of these, although the question will usually point you toward one particular pituitary abnormality. Remember that you are unlikely to elicit a galactorrhoea history unless you specifically ask and are sensitive about it.
- The pancreas tumours can be an insulinoma (persistent hypoglycaemia -check C-peptide which will be high in endogenous insulin secretion as opposed to exogenously given insulin e.g. in self harm/non-accidental injury, where c-peptide levels remain low. ), gastrinoma (Zollinger-Ellison, presenting as refractory gastric ulcers), glucagonoma causing persistent hyperglycaemia and also a necrolytic migratory erythema (as in this case), or a VIPoma causing profuse watery diarrhoea (VIP is the antagonist to gastrin and therefore tries to get you to flush the gut out rather than hold and digest contents).

MEN II has two forms. MEN2a presents with medullary thyroid carcinoma (neck lump), parathyroid tumour (hypercalcemia) and pheochromocytoma (hypertension, flushing, tachycardia intermittently). MEN2b presents with medullary thyroid carcinoma and pheochromocytoma.

The key message for the exam is that if you are presented with a case where you suspect there is an endocrine abnormality (even just a high calcium), look again at the stem to make sure you are not missing other endocrine abnormalities being present (e.g. amenorrhoea) that might alert you to there being an underlying diagnosis of MEN. If you know a few key features of each of the possible abnormalities within each type of MEN, you should be able to pinpoint which MEN type is present.

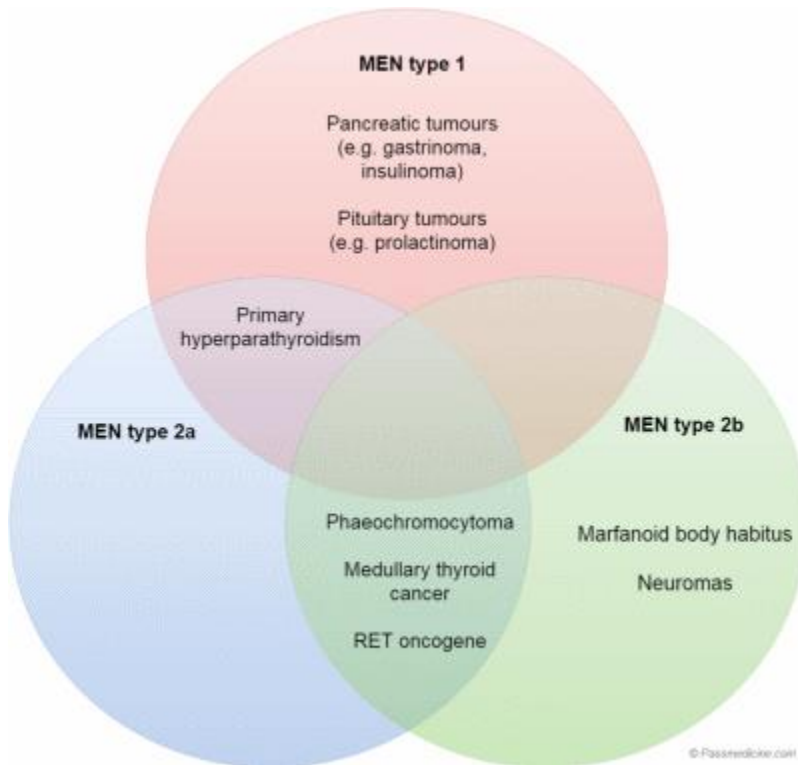
#### References:

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- <http://www.ncbi.nlm.nih.gov/pubmed/10843153>
- <http://www.endocrine-abstracts.org/ea/0029/ea0029MTE16.htm>

## Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	MEN type IIa	MEN type IIb
3 <b>P</b> 's <b>P</b> arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia <b>P</b> ituitary (70%) <b>P</b> ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration)	Medullary thyroid cancer (70%)  2 <b>P</b> 's <b>P</b> arathyroid (60%) <b>P</b> haeochromocytoma	Medullary thyroid cancer  1 <b>P</b> <b>P</b> haeochromocytoma  Marfanoid body habitus Neuromas
Also: adrenal and thyroid		
MEN1 gene	RET oncogene	RET oncogene
Most common presentation = hypercalcaemia		



Venn diagram showing the different types of MEN and their associated features

### Question 3 of 7

You are reviewing a 38-year-old woman with type 1 diabetes mellitus in clinic. Her diabetes is currently controlled with a basal-bolus regime. She takes no other medication apart from citalopram 20mg od for depression. She was diagnosed with type 1 diabetes at the age of 13 years. Her most recent bloods show

Na<sup>+</sup> 142 mmol/l

K<sup>+</sup> 3.9 mmol/l

Urea 4.9 mmol/l

Creatinine 79 µmol/l

Total cholesterol 4.4 mmol/l

HDL cholesterol 1.2 mmol/l

LDL cholesterol 1.8 mmol/l

Triglyceride 1.3 mmol/l

Urine dip: No protein or blood

What is the most appropriate management with regards to lipid modification?

[Start atorvastatin 10mg on6%](#)[Start atorvastatin 20mg on49%](#)[Start atorvastatin 40mg on7%](#)[Perform a QRISK2 assessment25%](#)[Reassure her that lipid modification therapy is not required at this stage13%](#)

NICE specifically state that we should not use QRISK2 for type 1 diabetics. Instead, the following criteria are used:

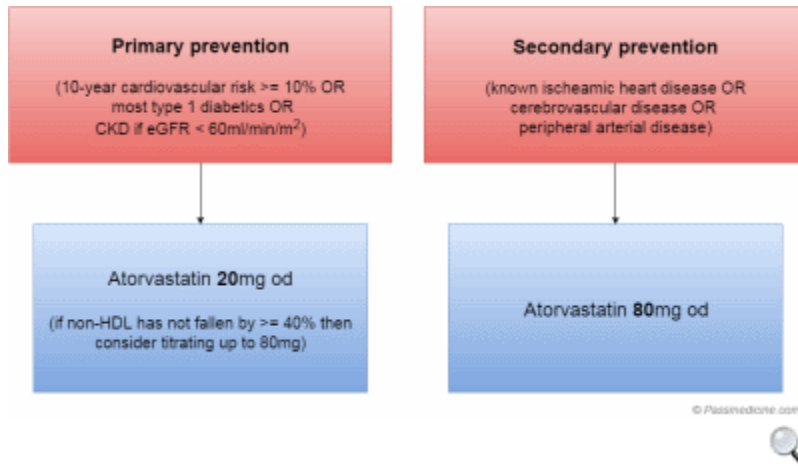
- older than 40 years, or
- have had diabetes for more than 10 years or
- have established nephropathy or
- have other CVD risk factors

This patient has had diabetes for 25 years so we should start atorvastatin 20mg on.

### Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as

it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.



Graphic showing choice of statin.

### Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged ≤ 84 years. Patients ≥ 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

### Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the



most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples does not need to be fasting.

In the vast majority of patient the cholesterol measurements will be fed into the QRISK2 tool. If however the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if the total cholesterol concentration is  $> 7.5$  mmol/l and there is a family history of premature coronary heart disease. They also recommend referring people with a total cholesterol  $> 9.0$  mmol/l or a non-HDL cholesterol (i.e. LDL) of  $> 7.5$  mmol/l even in the absence of a first-degree family history of premature coronary heart disease.

### **Interpreting the QRISK2 result**

Probably the headline changes in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

**NICE now recommend we offer a statin to people with a QRISK2 10-year risk of  $\geq 10\%$**

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

### **Special situations**

#### **Type 1 diabetes mellitus**

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - → older than 40 years, or
  - → have had diabetes for more than 10 years or
  - → have established nephropathy or
  - → have other CVD risk factors

#### **Chronic kidney disease (CKD)**

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR  $> 30$  ml/min. If the eGFR is  $< 30$  ml/min a renal specialist should be consulted before increasing the dose

## **Secondary prevention**

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

## **Follow-up of people started on statins**

NICE recommend we follow-up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

## **Lifestyle modifications**

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be  $\leq 30\%$  of total energy intake
- saturated fats should be  $\leq 7\%$  of total energy intake
- intake of dietary cholesterol should be  $< 300$  mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity

- do muscle strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

#### Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

#### Alcohol intake

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

#### Smoking cessation

- smokers should be encouraged to quit
- Question 1 of 4
- A 24 year-old woman presents to hospital after collapsing while out shopping. On taking her observations, she has a temperature 37.2°C, a pulse rate of 78 per minute which is regular and normal in character and a blood pressure of 164/92 mmHg. Heart sounds 1 and 2 were present with no added sounds and his chest was clear on auscultation. His abdomen was soft and non-tender with no organomegaly. Neurological examination was unremarkable. She has no past medical history of note and is on no regular medications.

Further blood tests reveal low renin and aldosterone levels, hypokalaemia and a serum bicarbonate of 30 mmol/l.

Which of the following is the most appropriate treatment for her condition?

- [Angiotensin converting enzyme inhibitor therapy6% Bumetanide7% Potassium replacement9% Spironolactone17% Amiloride61%](#)

- 

This woman has presented with the combination of hypokalaemic alkalosis, suppressed renin and aldosterone levels in the presence of hypertension indicates a diagnosis of Liddle syndrome. Hypertension and hypokalaemia respond well to amiloride. Spironolactone is not as effective as this medication acts on the mineralocorticoid receptor, as opposed to amiloride, which acts directly on the sodium channel.

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- **Liddle's syndrome**

- Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

Treatment is with either amiloride or triamterene

#### Question 4 of 4

A 42-year-old woman was seen in clinic with a history of palpitation, tremor and weight loss. There is no other past medical history and she takes no regular medication.

On examination, she had a palpable goitre, exophthalmos, and a tremor of the out-stretched hands.

Thyroid function tests showed:

Free thyroxine (T4) 36 pmol/L (10-25)

Free triiodothyronine (T3) 15 pmol/L (5-10)

Thyroid-stimulating hormone 0.1mU/L (0.4-5.0)

Which of the following treatments should be prescribed initially to improve symptoms?

[Thyroidectomy4%](#) [Propanolol70%](#) [Radioiodine ablation4%](#) [Carbimazole17%](#) [Propylthiouracil5%](#)

There is a high suspicion of Grave's disease in this patient, and further investigation with a thyroid autoantibody profile is warranted.

Beta blockers are used to treat the symptoms of increased beta-adrenergic tone that are seen in Grave's disease. Other such symptoms include anxiety and heat intolerance.

Thioamides are used to treat Grave's hyperthyroidism, but not specifically the symptoms of increased beta-adrenergic tone. While the anti-thyroid effect of these drugs has a rapid onset, their clinical effect is more delayed because the pre-formed store of hormone in the thyroid gland and bound to thyroid-binding globulin must first be exhausted.

#### **Graves' disease: management**

Despite many trials there is no clear guidance on the optimal management of Graves' disease. Treatment options include titration of anti-thyroid drugs (ATDs, for example carbimazole), block-and-replace regimes, radioiodine treatment and surgery. Propranolol is often given initially to block adrenergic effects

#### ATD titration

- carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime

#### Block-and-replace

- carbimazole is started at 40mg
- thyroxine is added when the patient is euthyroid
- treatment typically lasts for 6-9 months

The major complication of carbimazole therapy is agranulocytosis

#### Radioiodine treatment

- contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years. Thyroid eye disease is a relative contraindication, as it may worsen the condition
- the proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

## HEMATOLOGY

### Question 1 of 104

A 35-year-old patient with known sickle cell disease presents to the emergency department with new onset of left arm and facial weakness. The symptoms began earlier in the day. He is normally very careful with his sickle disease and ensures he is well hydrated and avoids the cold. His wife admits that over the last few days he has been suffering from nausea and vomiting and diarrhoea after he had a takeaway meal 3 days ago. On examination his observations are within normal parameters. He has slurred speech and an obvious left facial droop with forehead sparing. He has power of 0/5 in his left arm but is otherwise neurologically intact.

His blood test show:

Hb 100 g/l

Platelets  $330 \times 10^9/l$

WBC  $8.9 \times 10^9/l$

INR 1.0

Na<sup>+</sup> 138 mmol/l

K<sup>+</sup> 3.5 mmol/l

Urea 9.9 mmol/l

Creatinine 135  $\mu\text{mol/l}$

CRP 19 mg/L(<10)

Bilirubin 12  $\mu\text{mol/l}$

ALP 89 u/l

ALT 39 u/l

Albumin 39 g/l

He is seen by the stroke team who arrange an urgent CT head which is reported as normal. What is the appropriate treatment for this gentleman?

[Thrombolysis9%Aspirin11%Plasmapheresis17%Methylprednisolone5%Exchangetransfusion57%](#)

This gentleman has a cerebral vaso-occlusive episode as a result of his sickle cell disease. The treatment of choice in these situations is urgent and aggressive exchange transfusion followed by transfusions to maintain HbS <30%. Thrombolysis and aspirin are not in the management guidelines for acute stroke in this situation.

## **Sickle-cell crises: management**

### General management

- analgesia e.g. opiates
- rehydrate
- oxygen
- consider antibiotics if evidence of infection
- blood transfusion
- exchange transfusion: e.g. if neurological complications

### Question 2 of 104

A 72-year-old woman with breast cancer presents with a swollen, painful left calf. She is known to have metastases in the vertebral bodies and is taking denosumab as prophylaxis. A Doppler ultrasound is arranged which shows a proximal deep vein thrombosis on the left side. This is her first episode of venous thromboembolism. What is the most appropriate management?

[Warfarin for 3 months9%](#) [Warfarin for 6 months8%](#) [Low-molecular weight heparin for 3 months15%](#) [Low-molecular weight heparin for 6 months66%](#) [Dabigatran for 3 months3%](#)

Cancer patients with VTE - 6 months of LMWH

## **Deep vein thrombosis: diagnosis and management**

### **Diagnosis**

NICE published guidelines in 2012 relating to the investigation and management of deep vein thrombosis (DVT).

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

## Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

### Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

### If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

### If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
- a proximal leg vein ultrasound scan within 4 hours
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

## Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.



- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months

### **Further investigations and thrombophilia screening**

As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:

- a physical examination (guided by the patient's full history) and
- a chest X-ray and
- blood tests (full blood count, serum calcium and liver function tests) and urinalysis.

Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

### **Thrombophilia screening**

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

### Question 3 of 104

A 55-year-old lady is seen in the Emergency Department with haematemesis. She developed upper abdominal pain yesterday and began vomiting dark brown material about an hour ago. She has also passed some loose stools today. She recalls having a couple of similar episodes of abdominal pain over the last 2 months but much less severe and not associated with vomiting.

Her past medical history includes hypertension, high cholesterol, type 2 diabetes, atrial fibrillation and chronic back pain. Her medications are bisoprolol, ramipril, atorvastatin, metformin, sitagliptin, apixaban, paracetamol and codeine. She also admits to taking some other over-the-counter pain relief for her back in recent months. She took her regular morning medication 10 hours ago but has not had any since.

On examination her heart rate is 105 beats per minute and blood pressure is 112/88 mmHg. She looks clammy and pale. She is very tender in the epigastric region with guarding and normal bowel sounds. There is malena on rectal examination.

Bloods have been sent but are not yet available, though a haemoglobin on venous gas is 96 g/l.

She is started on fluids and an urgent endoscopy is requested. Which medication should be given to help control the bleeding?

[Activated charcoal and prothrombin complex concentrate6%](#)[Activated charcoal and tranexamic acid6%](#)[Prothrombin complex concentrate and tranexamic acid57%](#)[Vitamin K and prothrombin complex concentrate19%](#)[Vitamin K and fresh frozen plasma12%](#)

This lady has major bleeding on apixaban. Consensus guidelines suggest that this should initially be managed with tranexamic acid, with consideration of prothrombin complex concentrate if there is insufficient response.

In cases where apixaban has been ingested within 6 hours, activated charcoal can be administered but this would be inappropriate in a gastrointestinal bleed.

There is no evidence to support the use of fresh frozen plasma to reverse the effects of novel anticoagulants such as apixaban.

Vitamin K is used to reverse warfarin (as warfarin inhibits vitamin K dependent clotting factor synthesis) but it does not affect the function of direct factor Xa inhibitors such as apixaban.

Reference: Ward et al. Practical management of patient on apixaban: a consensus guide. Thrombosis Journal. 2013.

## Novel oral anticoagulants (NOACs)

The table below summaries the three NOACs: dabigatran, rivaroxaban and apixaban.

	<b>Dabigatran</b>	<b>Rivaroxaban</b>	<b>Apixaban</b>
<b>UK brand name</b>	Pradaxa	Xarelto	Eliquis
<b>Mechanism of action</b>	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
<b>Route</b>	Oral	Oral	Oral
<b>Excretion</b>	Majority renal	Majority liver	Majority faecal
	Prevention of VTE following hip/knee surgery	Prevention of VTE following hip/knee surgery	Prevention of VTE following hip/knee surgery
<b>NICE indications</b>	Treatment of DVT and PE  Prevention of stroke in non-valvular AF*	Treatment of DVT and PE  Prevention of stroke in non-valvular AF*	Treatment of DVT and PE  Prevention of stroke in non-valvular AF*

\*NICE stipulate that certain other risk factors should be present. These are complicated and differ between the NOACs but generally require one of the following to be present:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- heart failure

### Question 4 of 104

A 62-year-old man had a routine set of blood tests performed by his General Practitioner. These demonstrated an erythrocytosis (Packed Cell Volume 0.56) but no other abnormality. Further questioning by the GP found that the patient had no symptoms of hyperviscosity, was a non-smoker with no symptoms of daytime somnolence and took no regular medications. Past medical history included only a left knee hemiarthroplasty performed due to osteoarthritis.

Two weeks after the initial blood test, the patient's bloods were repeated and showed a persistence of the erythrocytosis. A referral to haematology clinic was made for further investigation. Details of further investigations arranged through haematology clinic are listed below.

Haemoglobin	188 g / L
White cell count	$6.7 \times 10^9/l$
Neutrophils	$3.2 \times 10^9/l$
Lymphocytes	$2.1 \times 10^9/l$
Monocytes	$0.8 \times 10^9/l$
Eosinophils	$0.3 \times 10^9/l$
Basophils	$0.3 \times 10^9/l$
Platelets	$202 \times 10^9/l$
Packed cell volume	0.59
Urea	4.5 mmol / L
Creatinine	97 micromol / L
Sodium	140 mmol / L
Potassium	3.9 mmol / L
eGFR	85 ml / min
Ferritin	80 ng / ml
Albumin	38 g / L
Alkaline phosphatase	89 U / L
ALT	25 U / L
Bilirubin	20 micromol / L
JAK 2 V617F mutation	Negative
Serum erythropoietin	0 U / L (reference 0-19)

Blood film: no abnormality detected; no features of myeloproliferative disease

Abdominal ultrasound: liver, hepatic duct system and gallbladder unremarkable; mild-moderate splenomegaly; kidneys and renal tract unremarkable

What is the most appropriate next investigation?

[JAK2 exon 12 mutation testing40%](#)  
[Bone marrow aspiration and trephine biopsy19%](#)  
[Measurement of red cell mass28%](#)  
[CT brain3%](#)  
[Erythropoietin receptor gene analysis10%](#)

Erythrocytosis is defined as a haemoglobin > 18.5 g / dL or PCV > 0.52 (male) / 0.48 (female). Patients with a persistent erythrocytosis without a clear cause (i.e. chronic hypoxia or drug causes) should be referred to haematology for further investigation. An urgent referral should be made if symptoms of hyperviscosity or polycythaemia (raised PCV, white cells and platelets) are present.

More than 95 % of individuals with polycythaemia vera test positive for the JAK 2 V617F mutation. Other baseline investigations include a blood film to exclude myeloproliferative disease, renal and liver profiles and serum ferritin (as iron deficiency can mask the degree of

erythrocytosis). Abdominal ultrasound is performed in patients with high suspicion for polycythaemia vera as this condition is associated with radiographical splenomegaly in two-thirds of cases.

A low serum erythropoietin is suggestive of primary bone marrow disease even in the absence of JAK 2 mutation and should prompt testing for the rarer exon 12 mutation of JAK 2. This test should be performed before the more invasive bone marrow biopsy.

Raised serum erythropoietin should prompt investigation for an exogenous source, for example, CT brain to look for a cerebellar haemangioma or meningioma.

In patients without a JAK 2 mutation and a normal erythropoietin level then measurement of red cell mass will distinguish between a true erythrocytosis and an apparent erythrocytosis (normal red cell mass but reduced plasma volume).

Rare congenital mutations in the erythropoietin receptor can also cause a primary erythrocytosis. Keohane C, McMullin M, Harrison C. The diagnosis and management of erythrocytosis. *BMJ* 2013;347:f6667.

## **Polycythaemia vera: features**

Polycythaemia vera (previously called polycythaemia rubra vera) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with polycythaemia vera and this has resulted in significant changes to the diagnostic criteria. The incidence of polycythaemia vera peaks in the sixth decade.

### **Features**

- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance
- hypertension in a third of patients

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

Other features that may be seen in PRV include a low ESR and a raised leukocyte alkaline phosphatase

The diagnostic criteria for polycythaemia vera have recently been updated by the BCSH. This

replaces the previous polycythaemia vera Study Group criteria.

JAK2-positive polycythaemia vera - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit ( $>0.52$ in men, $>0.48$ in women) OR raised red cell mass ( $>25\%$ above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass ( $>25\%$ above predicted) OR haematocrit $>0.60$ in men, $>0.56$ in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count $>450 \times 10^9/l$ )
B2	Neutrophil leucocytosis (neutrophil count $> 10 \times 10^9/l$ in non-smokers; $> 12.5 \times 10^9/l$ in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

#### Question 5 of 104

A 54-year-old gentleman is reviewed 48 hours after being admitted to his local hospital with neutropaenic sepsis. He measured his temperature at home found it to be  $38.2^{\circ}\text{C}$ . Because of this, he called the chemotherapy helpline and he was advised to attend the emergency department who promptly admitted him under the care of the medical team.

He has a background of metastatic colorectal cancer and he has had chemotherapy ten days ago. He was started on piperacillin with tazobactam on admission. His temperature settled within 12 hours and investigations, including blood cultures, a chest X-ray, urine testing and a thorough examination did not find any source of infection. His initial neutrophil count was  $0.4 \times 10^9/l$ . Recent blood tests demonstrate a neutrophil count of  $0.5 \times 10^9/l$ . His vital parameters have all been normal since his temperature settled and he has not noticed any symptoms at any point.

What is the most appropriate management plan?

Convert patient to oral antibiotics and discharge 34% Keep on IV antibiotics in hospital until full course completed 20% Monitor neutrophil count in hospital and discharge when greater than  $1 \times 10^9$  134% Arrange for outpatient IV antibiotics 6% Change piperacillin with tazobactam to meropenem 6%

The correct answer is to convert patient to oral antibiotics and discharge. This is a patient who was admitted with a fever and a low neutrophil count and therefore he was managed with empirical IV antibiotics for neutropenic sepsis. Many of these patients will not look or feel significantly unwell and in the majority of them identifying a source of the temperature can be impossible. If neutropenic they should be treated with urgent IV antibiotics and waiting for a full blood count to confirm the low neutrophil count would be inappropriate. At 48 hours the antibiotic should be reviewed and if still febrile then escalation of antibiotics should be considered. If they have improved and the temperature has settled then there can be a consideration of an oral switch or if completely well can stop antibiotics altogether. NICE does not recommend keeping patients in hospital whilst waiting for their neutrophil count to improve.

Source:

'Neutropenic sepsis: prevention and management in people with cancer.' Clinical guideline [CG151]. The National Institute for Health and Care Excellence, September 2012.

## Neutropenic sepsis

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy. It may be defined as a neutrophil count of  $< 0.5 \times 10^9$  in a patient who is having anticancer treatment and has one of the following:

- a temperature higher than  $38^\circ\text{C}$  or
- other signs or symptoms consistent with clinically significant sepsis

## Prophylaxis

- if it is anticipated that patients are likely to have a neutrophil count of  $< 0.5 \times 10^9$  as a consequence of their treatment they should be offered a fluoroquinolone



## Management

- antibiotics must be started immediately, do not wait for the WBC
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

## Question 6 of 104

A 28-year-old man is admitted to the Medical Admissions Unit with a 2-day history of itching, right upper quadrant pain, and abdominal distension. The pain started as a dull ache but became constant and severe over the course of several hours.

His past medical history is remarkable only for a left lower limb DVT diagnosed at age 20. He takes no regular medications and he is a non-smoker. He drinks 2-3 units of alcohol per week and denies intravenous drug use.

Examination reveals a jaundiced young man with pale conjunctivae. He appears deeply uncomfortable. His abdomen is moderately distended with marked right upper quadrant tenderness. His liver and spleen are both palpable 2cm below the costal margin. Shifting dullness is demonstrable on percussion of the abdomen.

His blood results are as follows:

Hb	101 g/l	Na <sup>+</sup>	139 mmol/l	Bilirubin	109 μmol/l
MCV	102.4 fl	K <sup>+</sup>	4.2 mmol/l	ALP	284 u/l
Platelets	63 * 10 <sup>9</sup> /l	Urea	6.7 mmol/l	ALT	684 u/l
WBC	12.9 * 10 <sup>9</sup> /l	Creatinine	108 μmol/l	γGT	179 u/l
Neuts	10.8 * 10 <sup>9</sup> /l			Albumin	27 g/l
Lymphs	0.9 * 10 <sup>9</sup> /l			LDH	759 u/l

His abdominal ultrasound scan is consistent with hepatic vein thrombosis and the patient is started on low molecular weight heparin. Following a review by the Haematologists, a diagnosis of paroxysmal nocturnal haemoglobinuria is made and the patient is advised to start treatment with eculizumab.

Given the proposed treatment strategy, which of the following vaccinations should the patient be offered?

[Hepatitis B 16%](#) [Neisseria meningitidis 33%](#) [Varicella zoster virus 13%](#) [Streptococcus pneumoniae 20%](#) [Haemophilus influenzae type b 18%](#)

Eculizumab is a recombinant humanised monoclonal antibody that specifically binds to terminal complement protein C5. Patients with C5 deficiency are at elevated risk of serious meningococcal infections and all patients being treated with eculizumab should receive a quadrivalent vaccine against the meningococcal strains A, C, W, and Y.

## **Paroxysmal nocturnal haemoglobinuria**

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

### **Pathophysiology**

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

### **Features**

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

## Diagnosis

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

## Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

### Question 1 of 97

A 26-year-old gentleman presents to haematology clinic one week prior to starting chemotherapy for acute myeloid leukaemia (AML). He is currently feeling fatigued, suffering from night sweats, and has chronic lower back pain. He is anxious to start treatment. His past medical history includes ankylosing spondylitis and a clavicular fracture. His current medications include paracetamol and ibuprofen.

#### Blood tests:

Hb	113 g/l
Platelets	$156 \times 10^9/l$
WBC	$57 \times 10^9/l$
Na <sup>+</sup>	140 mmol/l
K <sup>+</sup>	3.6 mmol/l
Urea	4.2 mmol/l
Creatinine	63 $\mu$ mol/l

What measure is the least useful to prevent tumour lysis syndrome?

[IV fluids prior to chemotherapy100%Urine alkalization0%Prophylactic allopurinol0%Prophylactic rasburicase0%Stopping NSAID use0%](#)

This patient has AML with a high white cell count and is about to start chemotherapy, and is therefore at high risk of tumour lysis syndrome (TLS). The key is to prevent TLS, which is done

by ensuring good renal perfusion. Commonly this can be done by aggressive intravenous hydration prior to the start of treatment and stop NSAIDs, such as ibuprofen for this patient. Allopurinol and rasburicase both prevent uric acid accumulation and can, therefore, be used as well. Urine alkalization has not shown to be effective.

Source:

Larson, Richard A., and Ching-Hon Pui. 'Tumor Lysis Syndrome: Prevention and Treatment.' UpToDate. N.p., 4 Oct. 2016.

## **Tumour lysis syndrome**

Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high grade lymphomas and leukaemias. It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. On occasion it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys. Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.

TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a low calcium. It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system -  
Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy.

- uric acid > 475umol/l or 25% increase
- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:

- increased serum creatinine (1.5 times upper limit of normal)
- cardiac arrhythmia or sudden death
- seizure

#### Question 2 of 97

A 43 year old man is brought to the Emergency Department by his wife. She has become worried about him in the past six months as he has become increasingly confused, aggressive and depressed. He has also lost 4kg in weight in this time and has developed severe, intermittent abdominal pain and diarrhoea, and complains of constant headaches.

Examination reveals a normal cardiorespiratory examination but the abdomen is diffusely tender and there is tender fullness in the right upper quadrant. Neurological examination reveals minor hypotonia throughout and there are bilateral radial nerve palsies as well as a left common peroneal nerve palsy. Sensation appears intact. He is alert but confused with an abbreviated mental test score of 7/10.

Blood tests reveal:

Sodium	136mmol/L	ALP	135U/L	Haemoglobin	79g/L
Potassium	5.1mmol/L	AST	265U/L	MCV	101fL
Urea	7.1mmol/L	ALT	298U/L	White cells	$9.4 \times 10^9/L$
Creatinine	102 $\mu$ mol/L	GGT	197U/L	Neutrophils	$5.6 \times 10^9/L$
CRP	10mg/L	Bilirubin	12 $\mu$ mol/L	Lymphocytes	$3.1 \times 10^9/L$
Calcium (corr)	2.34mmol/L			Eosinophils	$0.1 \times 10^9/L$
Phosphate	0.56mmol/L			Basophils	$0.6 \times 10^9/L$
Magnesium	0.76mmol/L				
Glucose	3.8mmol/L				

The blood film shows anaemia with a dimorphic picture, significant reticulocytosis and high basophil numbers with cytoplasmic stippling.

The patients wife tells you all the symptoms coincided with the patient starting a new job as a loading crane driver at a scrap-yard.

What is the most likely diagnosis?

[Chronic alcoholism6%](#) [Acute promyelocytic leukaemia6%](#) [Porphyria cutanea tarda10%](#) [Chronic lead poisoning72%](#) [Minimata disease7%](#)

Lead poisoning is often occupational and comprises gastrointestinal and neuropsychiatric symptoms and anaemia due to interruption to the haem biosynthetic pathway. Wrist drop is a pathognomonic sign

The above vignette gives a classical description of chronic lead poisoning, also known as plumbism or Devon colic. The typical signs are gastrointestinal and neuropsychiatric and include severe, colicky abdominal pain with weight loss and diarrhoea and a metallic taste in the mouth. Insidious neurological signs include headache, difficulty concentrating, subtle personality changes including aggression and difficulty sleeping, dyspraxia and cerebellar signs. The pathognomonic hallmark of chronic lead poisoning is a radial nerve palsy, or wrist drop, although many peripheral nerve palsies may be seen. Patients may also have a bluish discolouration to their skin and a blue line on the gums, known as Burton's line, is very rarely seen. Biochemically, a hepatitic picture can be seen and also occasionally renal impairment due to proximal renal tubular failure, particularly with increased excretion of phosphate and glucose and acidification of the urine. However, most notable is the haematological impact of lead poisoning with a pronounced anaemia, often with dimorphic picture and reticulocytosis due to arrest of the haem biosynthetic pathway. Basophilia with stippling is seen and bone marrow trephine may show ring sideroblasts.

Blood lead levels do not correlate well with total lead burden and the diagnosis may be missed due to incorrect assay or test selection. Since lead is concentrated in red cells, whole blood levels of lead rather than plasma must be analysed, however testing for enzymes affected by lead is more reliable than whole lead levels alone, and hence erythrocyte zinc protoporphyrin (ZPP) levels and delta aminolevulinic acid dehydratase (ALAD) are more reliable. These, coupled with skeletal analysis and blood lead levels are used to test for occupational lead poisoning. The term metal fume fever is used to describe many syndromes of heavy metal and metal oxide poisonings, often in gantry crane drivers who deposit scrap metals in furnaces from above. Many scrap metals are coated in lead based paints leading to occupational lead toxicity syndromes.

Lead poisoning is clinically similar to porphyria and pathologically an interruption in haem pathways are seen in both. The classical hallmark of porphyria cutanea tarda is a blistering photosensitive rash that is not present in this case. Chronic alcoholism may cause B12 deficiency and hence a megaloblastic anaemia and confusion but it is unlikely to cause this constellation of neuropathies and does not explain the basophilic stippling. There is no mention of the patient's alcohol habits either. An acute promyelocytic leukaemia presents with non specific symptoms and infections. It may present with sudden onset neurological symptoms only if there is a spontaneous intracranial bleed, in which case the outlook is bleak. It is unlikely here. Minamata disease is an acute mercury toxicity and presents with neuropsychiatric symptoms and rapid death. It would not be expected to cause the haematological picture seen here.

## **Lead poisoning**

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs

#### Features

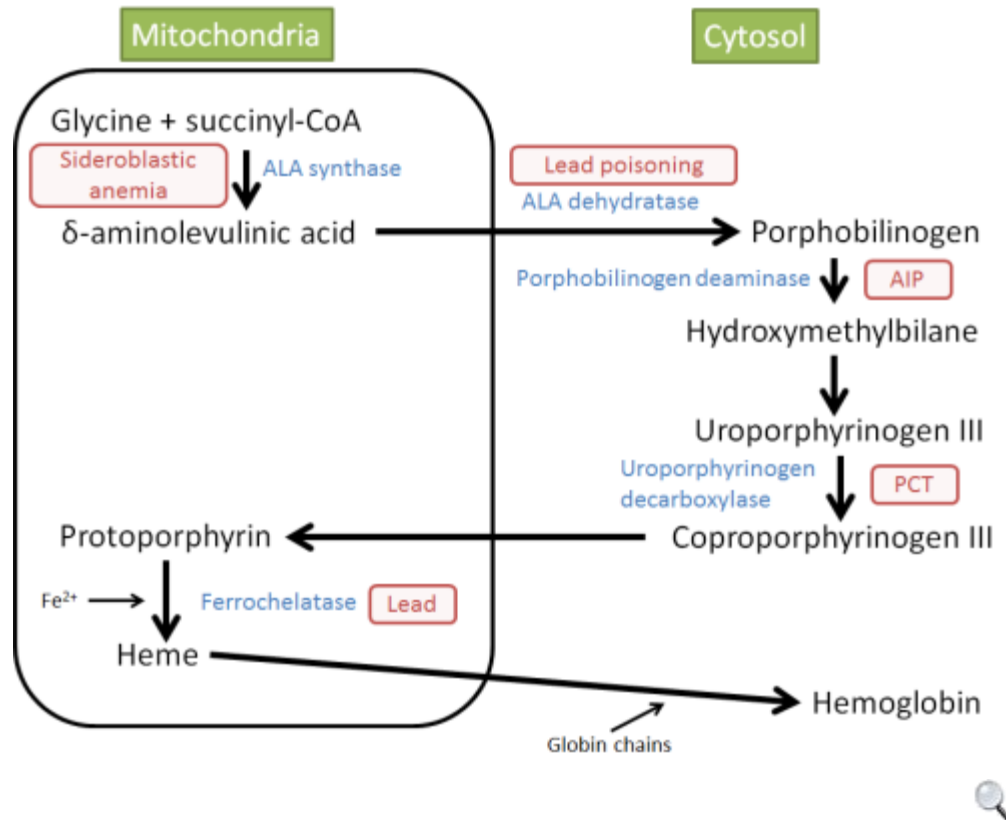
- abdominal pain
- peripheral neuropathy (mainly motor)
- fatigue
- constipation
- blue lines on gum margin (only 20% of adult patients, very rare in children)

#### Investigations

- the blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- full blood count: microcytic anaemia. Blood film shows red cell abnormalities including basophilic stippling and clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA
- dimercaprol



### Question 3 of 97

A 24-year-old man undergoing his second cycle of ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) chemotherapy for Hodgkin lymphoma feels tired and short of breath on exertion. His temperature is 36.5°C and he reports no bleeding.

Bloods show:

Hb 69 g/L  
WCC  $1 \times 10^9$  /L  
Neutrophils  $0.7 \times 10^9$  /L  
Platelets  $19 \times 10^9$  /L

What is the most appropriate treatment?

[CMV negative blood 9%](#) [Phenotyped blood 4%](#) [Irradiated blood 33%](#) [CMV negative and irradiated blood 46%](#) [Leucodepleted blood 8%](#)

Guidance has recently changed regarding the uses of CMV negative blood. The indications for



CMV negative blood are for pregnant patients, intrauterine transfusions and neonates. Indications for irradiated blood include Hodgkin lymphoma, a previous purine analogue, stem cell transplant, HLA matched products. Indications for phenotyped blood include sickle cell disease and patients with clinically significant antibodies. All blood products are leucodepleted; this does not have to be requested. Platelets are not required as the patient is afebrile and not bleeding.

### **Blood products: CMV negative and irradiated blood**

Cytomegalovirus (CMV) is transmitted in leucocytes. As most blood products (except granulocyte transfusions) are now leucocyte depleted CMV negative products are rarely required.

Irradiated blood products are used to avoid transfusion graft versus host disease (TA-GVHD) caused by engraftment of viable donor T lymphocytes.

The table below shows the indications for CMV and irradiated blood:

<b>Situation</b>	<b>CMV negative</b>	<b>Irradiated</b>
Granulocyte transfusions	✓	✓
Intra-uterine transfusions	✓	✓
Neonates up to 28 days post expected date of delivery	✓	✓
Pregnancy: Elective transfusions during pregnancy (not during labour or delivery)	✓	
Bone marrow / stem cell transplants		✓
Immunocompromised (e.g. chemotherapy or congenital)		✓
Patients with/previous Hodgkins Disease		✓
HIV		

Question 4 of 97

A 50-year-old lady presents to the emergency department with transient left sided facial droop and arm weakness lasting 30 minutes with expressive dysphasia which has resolved by the time

she arrives in the department. She is referred to the medical team because she has a fever of 38.2 degrees Celsius and has been otherwise generally unwell for the last few days. She is seen by the stroke nurse who arranges for her to have a CT head which is reported as normal. Her blood results are as follows;

Hb 82 g/l  
Platelets  $12 \times 10^9/l$   
WBC  $5.0 \times 10^9/l$   
Neutrophils  $3.0 \times 10^9/l$   
Blood film multiple red cells fragments

Na<sup>+</sup> 138 mmol/l  
K<sup>+</sup> 4.8 mmol/l  
Urea 8.0 mmol/l  
Creatinine 180  $\mu$ mol/l

Bilirubin 78  $\mu$ mol/l  
ALP 78 u/l  
ALT 40 u/l  
Albumin 38 g/l

She is transferred to the acute medical unit. Whilst on the ward awaiting a haematology review for her low platelets and anaemia she suffers another TIA. Given the likely cause of her symptoms, what is the most appropriate treatment?

[Aspirin5%Methylprednisolone and plasma exchange80%Thrombolysis5%High dose cyclophosphamide6%Haemodialysis5%](#)

This lady is suffering from TTP; she has a fever, fluctuating neurological signs, with acute kidney injury, thrombocytopenia and haemolysis. The treatment for TTP is high-dose methylprednisolone for 3 days and plasma exchange daily until platelet counts return to normal. Thrombolysis is not appropriate here due to the aetiology and low platelet count. Aspirin would be the correct answer if this were a simple TIA but given the clinical picture a simple TIA is unlikely.

**Thrombotic thrombocytopenic purpura: management**

## Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

## Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

## Question 5 of 97

A 28-year-old Afro-Caribbean male presents with a two-hour history of sudden onset left sided weakness. He denies any sensory involvement, dysarthria or dysphasia. He has a known history of sickle cell disease, with two previous episodes of transient ischaemic attacks and an episode of acute chest syndrome attack 10 days ago. On examination, he displays power of 1/5 in his left arm, 2/5 in his left leg, 5/5 in his right side. He reports no sensory disturbances, plantar responses are downgoing bilaterally, he is unable to perform finger-nose testing. He denies any illicit drug use, is a non-smoker and does not drink alcohol. He has no other past medical history. A hyperacute CT head demonstrates an area of acute ischaemia in the right internal capsule region. What is the most appropriate immediate treatment?

[Intravenous thrombolysis17%Aspirin 300mg12%Intravenous thrombolysis and mechanical thrombectomy11%Exchange transfusion55%Clopidogrel 300mg5%](#)

This patient has presented with an acute vaso-occlusive crisis on a background of known sickle cell disease. He is at high risk of an infarctive stroke given the background of previous TIAs (increased relative risk by 56 times) and a recent chest crisis within the past 2 weeks (increased relative risk by 7 times). The other risk factors include a high systolic pressure (RR 1.3 increase per 10mmHg) and a low steady state haemoglobin (RR 1.9 per 1g/dL decrease)<sup>1</sup>. The management of an acute sickle infarct is different to that of thromboembolic stroke or atheromatous disease. The immediate aim is to reduce the proportion of HbS, either with immediate transfusion or optimally, with exchange transfusion. The latter reduces the concentration of HbS faster with a lower risk of transfusional volume overload, possibly resulting in increased blood viscosity and consequent pulmonary oedema.

1. Ohene-Frempong K, Weiner SJ, Sleeper LA et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288

## **Sickle-cell crises: management**

### General management

- analgesia e.g. opiates
- rehydrate
- oxygen
- consider antibiotics if evidence of infection
- blood transfusion
- exchange transfusion: e.g. if neurological complications

### Question 6 of 97

A 33-year-old patient presents to the emergency department feeling very lethargic and tired over the last week. He has been increasingly short of breath on exertion and his exercise tolerance has fallen to a few hundred yards before he is out of breath. He is a known sickle cell disease patient who is managed by the Haematology team in your hospital. On examination he is afebrile and heart rate and blood pressure are within normal limits. His respiratory rate is 16/min and his oxygen saturation is 98% on air. He does become noticeably short of breath on minimal movement.

His blood tests show:

Hb	65 g/l
Platelets	$46 \times 10^9/l$
WBC	$2.5 \times 10^9/l$
Neuts	$1.2 \times 10^9/l$
Haptoglobins	1.9 g/L (0.3-2.0)
Reticulocytes	$8.9 \times 10^9/L$ (25-80)
Na <sup>+</sup>	136 mmol/l

K<sup>+</sup> 3.9 mmol/l  
Urea 7.4 mmol/l  
Creatinine 78 µmol/l  
CRP <3 mg/L(<10)  
LDH 200 IU/L (200-500)

Bilirubin 4 µmol/l  
ALP 89 u/l  
ALT 34 u/l  
Albumin 39 g/l

His chest x-ray is normal.

On further questioning, he tells you that his 5-year-old daughter was unwell 3 weeks ago. He took her to see the GP and was told it was likely to be a viral illness. What is the most likely cause for his blood results as shown?

[Parvovirus B19 83% Acute chest crisis 5% Splenic sequestration 6% HIV 3% Legionella pneumoniae 3%](#)

This gentleman has had an aplastic sickle cell crisis as a result of parvovirus infection. He has symptomatic anaemia. There is nothing to suggest splenic sequestration and he is too well for an acute chest syndrome. The normal chest x-ray is not in keeping with a pneumonia. HIV is a possibility but less likely given the clinical picture.

## **Sickle-cell crises**

Sickle cell anaemia is characterised by periods of good health with intervening crises

Four main types of crises are recognised:

- thrombotic, 'painful crises'
- sequestration
- aplastic
- haemolytic

Thrombotic crises

- also known as painful crises or vaso-occlusive crises
- precipitated by infection, dehydration, deoxygenation
- infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain)

#### Sequestration crises

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO<sub>2</sub> - the most common cause of death after childhood

#### Aplastic crises

- caused by infection with parvovirus
- sudden fall in haemoglobin

#### Haemolytic crises

- rare
- fall in haemoglobin due an increased rate of haemolysis

#### Question 1 of 91

A 54-year-old woman presents to the emergency department. She has noticed a sore throat over the last 24 hours and checked her temperature and found it to be 38.2°C. Her other observations are all normal. She has had no other symptoms and specifically denies coughing, chest pain, dysuria and diarrhoea. She is currently undergoing chemotherapy for breast cancer having last had treatment six days ago. What is the most appropriate treatment?

[Confirm neutropenia before treatment23%IV co-amoxiclav and oral clarithromycin6%Oral metronidazole5%IV piperacillin with tazobactam61%IV gentamicin4%](#)

The correct answer is IV piperacillin with tazobactam. This is a patient who is likely to have a low neutrophil count as she has recently had chemotherapy. Such patients should be treated as neutropenic sepsis if there is a temperature above 38°C or any other sign of sepsis, and need immediate IV piperacillin with tazobactam. Some units use vancomycin as well at this point. This should be given before confirming the neutropenia as that would cause an unnecessary delay. IV gentamicin would be generally used for pyelonephritis, whilst IV co-amoxiclav and

oral clarithromycin would be used for a severe community acquired pneumonia.

Source:

'Neutropenic sepsis: prevention and management in people with cancer.' NICE guideline [CG151]. The National Institute for Health and Care Excellence, September 2012.

## **Neutropenic sepsis**

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy. It may be defined as a neutrophil count of  $< 0.5 \times 10^9$  in a patient who is having anticancer treatment and has one of the following:

- a temperature higher than 38°C or
- other signs or symptoms consistent with clinically significant sepsis

## **Prophylaxis**

- if it is anticipated that patients are likely to have a neutrophil count of  $< 0.5 \times 10^9$  as a consequence of their treatment they should be offered a fluoroquinolone

## **Management**

- antibiotics must be started immediately, do not wait for the WBC
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

## Question 2 of 91

A 16-year-old female was admitted with new onset facial swelling. The facial swelling started 45 minutes ago and initially involved her lips. She complained of a sensation of choking and a feeling of being unable to speak with hoarseness of her voice. She had been investigated on multiple occasions for abdominal pain and was diagnosed with non-specific abdominal pain. She was not taking any medication and was otherwise healthy prior to the admission.

She was given prednisolone 40mg PO and chlorpheniramine 10mg PO and admitted for observation. Whilst in the department she developed profound shortness of breath with associated stridor. Her swelling around her lips worsened and involved the whole of her face. On examination, she was in respiratory distress with severe biphasic stridor. Her respiratory rate was 32/min with an oxygen saturation of 88% on air. Auscultation of her chest also revealed the presence of a widespread polyphonic wheeze. Examination of her cardiovascular system revealed the presence of flushed peripheries with a bounding peripheral pulse. Her pulse was 102bpm and her blood pressure was 92/68 mmHg. Her GCS was 15 and neurological and abdominal examinations were unremarkable. She was cannulated and commenced on stat intravenous colloid solution. She was given adrenaline 0.5mg IM on three separate occasions within 10 minutes with no improvement. She was transferred immediately to the Intensive Care Unit and an anaesthetist fast bleeped to secure her airway.

What is the best immediate management step pending definitive airway management?

[Commence IV adrenaline infusion 11%](#)[Commence danazol 6%](#)[Commence IV dopamine 3%](#)[Commence fresh frozen plasma infusion 7%](#)[Commence C1 esterase inhibitor concentrate infusion 73%](#)

This patient has hereditary angioedema. This condition is characterised by a lack of C1 esterase inhibitor and may present with laryngeal oedema, recurrent abdominal pain and localised subcutaneous swelling. Laryngeal oedema may be fatal, does not respond to glucocorticoids or antihistamines, and has an only modest response to adrenaline. The immediate management is to commence C1 esterase inhibitor concentrate infusion. Fresh frozen plasma infusion may be administered if the concentrate is not available. Danazol is more suitable for subcutaneous oedema or as prophylaxis in certain situations eg prior to surgery.

## Hereditary angioedema

Hereditary angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in oedema of



tissues.

### Investigation

- C1-INH level is low during an attack
- low C2 and C4 levels are seen, even between attacks. Serum C4 is the most reliable and widely used screening tool

### Symptoms

- attacks may be preceded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)
- urticaria is not usually a feature

### Management

- acute: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help

### Question 3 of 91

A 22-year-old man with sickle cell disease is seen in the Emergency Department. He has had worsening pain in his arms and legs for the last 2 days and 5 hours ago developed a painful sustained erection.

He has felt otherwise well recently and has no other past medical history. He is on regular paracetamol, ibuprofen, folate and penicillin. He does not receive regular transfusions and has been admitted with a crisis only once before. He has never had an episode of painful sustained erection.

On examination he has a heart rate of 110 beats per minute and a blood pressure of 132/95 mmHg. His oxygen saturations are 96% on room air and he is afebrile. His chest is clear and abdomen is soft. He has no swelling or erythema of his limbs, though they are generally tender. He continues to have an erection, though there is no sign of ischaemia.

His chest x-ray shows clear lung fields.

His blood tests are as follows:

Hb	78 g/l	Na <sup>+</sup>	141 mmol/l
Platelets	331 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.7 mmol/l
WBC	9 * 10 <sup>9</sup> /l	Urea	5 mmol/l
Neuts	7 * 10 <sup>9</sup> /l	Creatinine	86 µmol/l
Lymphs	1.6 * 10 <sup>9</sup> /l	CRP	14 mg/l

He is treated with intravenous fluids and generous analgesia with diamorphine. His limb pain is improved but he continues to have a painful erection.

What is the next most appropriate step?

[Adrenalin6%Diethylstilbestrol14%Exchange transfusion38%Review by urologist34%Sildenafil8%](#)

This gentleman has priapism, a sustained painful erection lasting 4 hours. If left untreated it can result in impotence. Current guidelines recommend initial conservative management with fluids and analgesia. Although any interventions beyond this have variable results, evidence supports prompt urology review to determine the need for surgical management including drainage. There is insufficient evidence to recommend routine exchange transfusions. Sildenafil, diethylstilbestrol and adrenalin may be used in consultation with urology but evidence of benefit is variable.

Reference - NIH Evidence-based management of sickle cell disease expert panel report 2014

## Sickle-cell crises

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- sequestration
- aplastic
- haemolytic

### Thrombotic crises

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#### Sequestration crises

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#### Aplastic crises

- caused by infection with parvovirus
- sudden fall in haemoglobin

#### Haemolytic crises

- rare
- fall in haemoglobin due an increased rate of haemolysis

#### Question 4 of 91

A 34-year-old male presents with a 4 day history of bloody diarrhoea and vomiting, fevers and associated with occasional abdominal cramps. He reports no other symptoms. He reports no previous history of gastrointestinal disease; there is no family history of inflammatory bowel disease. He has no past medical history except for a left knee arthroscopy following an injury playing football 7 months ago. He is a lifelong non-smoker, drinks 14 units of alcohol a month, has not travelled abroad in the past year and last ate outside of his home a week ago during a barbecue at his brother's house.

On examination, he appears dehydrated. There is mild generalised abdominal tenderness with increased bowel sounds. Respiratory and cardiovascular examinations were unremarkable. His blood tests are as follows:

Hb	92 g/l
MCV	90fl
Platelets	49 * 10 <sup>9</sup> /l
WBC	14.2 * 10 <sup>9</sup> /l

Neutrophils	12.8 * 10 <sup>9</sup> /l
Blood film	schistocytes, reticulocytosis
Direct antiglobulin test	negative
Urea	14.9 mmol/l
Creatinine	159 µmol/l
CRP	82 mg/l

What is the cause of this patient's blood abnormalities?

[Microangiopathic haemolytic anaemia 68%](#)[Cold autoimmune haemolytic anaemia 1%](#)[Warm autoimmune haemolytic anaemia 12%](#)[Iron deficiency anaemia 4%](#)[Acute myeloid leukaemia 5%](#)

The first recognition in this patient is the underlying syndrome: blood film with fragment red cells (schistocytes), thrombocytopaenia acute kidney injury, pyrexia and bloody diarrhoea, should strongly suggest haemolytic uraemia syndrome-thrombotic thrombocytopaenia purpura spectrum (HUS-TTP) in the absence of alternative unifying causes. In this case, gastrointestinal infection by *Campylobacter* from the recent barbecue, producing Shiga toxins and resulting in endothelial damage, is a strong possible culprit. The patient has a normocytic anaemia with red cell fragmentation and increased reticulocyte production, suggestive of rapid mechanical destruction and the bone marrow releasing immature red cells in (unsuccessful) compensation. This represents microangiopathic haemolytic anaemia (MAHA) in the context of HUS-TTP.

Both cold and warm autoimmune haemolytic anaemias should produce a positive direct antiglobulin test (Coombs): addition of a Coombs reagent containing antihuman globulin should agglutinate red cells IgM and IgG antibodies bound to in cold and warm autoimmune haemolytic anaemias respectively. Iron deficiency anaemia typically produces microcytic anaemias with target cells; there are no blast cells suggestive of leukaemia.

## Haemolytic anaemias: by cause

**Hereditary haemolytic anaemias** can be subdivided into membrane, metabolism or haemoglobin defects

Hereditary causes

- membrane: hereditary spherocytosis/elliptocytosis
- metabolism: G6PD deficiency
- haemoglobinopathies: sickle cell, thalassaemia

**Acquired haemolytic anaemias** can be subdivided into immune and non-immune causes

Acquired: immune causes

- autoimmune: warm/cold antibody type
- alloimmune: transfusion reaction, haemolytic disease newborn
- drug: methyl dopa, penicillin

Acquired: non-immune causes

- microangiopathic haemolytic anaemia (MAHA): TTP/HUS, DIC, malignancy, pre-eclampsia
- prosthetic cardiac valves
- paroxysmal nocturnal haemoglobinuria
- infections: malaria

Question 5 of 91

A 42-year-old man with no past medical history of note and on no medications presents with complaints of dark-red urine during the night or early morning. His urine becomes clear during the day. He is otherwise asymptomatic. Urine dipstick is positive for blood but microscopy comes back as not showing any red blood cells. Clinical examination is unremarkable. His blood profile shows a mild macrocytic anaemia with an elevated reticulocyte count and he has an International Normalised Ratio (INR) of 7. Which of the following should be included in your management of the suspected condition?

[Warfarin25%](#) [Tranexamic acid21%](#) [Imatinib16%](#) [Aspirin19%](#) [Splenectomy19%](#)

Paroxysmal nocturnal haemoglobinuria (PNH) is a thrombotic condition that will paradoxically raise INR and APTT. Thromboprophylaxis is required. The question may throw certain candidates who feel he may be bleeding (haematuria), particularly with a raised INR. However, there is no evidence of bleeding in this example and he is at risk of clots. The macrocytic anaemia with an elevated reticulocyte count tells you there is a haemolytic process occurring (PNH results in intravascular haemolysis). There may be associated low platelets/white cell counts as PNH is haematopoietic stem cell disorder which results in the formation of defective red cells, white cells and platelets.

Reference/further reading: <https://www.ncbi.nlm.nih.gov/pubmed/27570707>

## **Paroxysmal nocturnal haemoglobinuria**

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

### **Pathophysiology**

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

### **Features**

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

### **Diagnosis**

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

### **Management**

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

### Question 6 of 91

A 29-year-old man who is known to be HIV positive is reviewed. He has been taking anti-retroviral therapy for the past 2 years and has remained relatively well. Over the past few weeks however he has developed abdominal distension with some discomfort in the right iliac fossa. On examination a mass can be felt in the right lower quadrant. A biopsy shows a B cell lymphoma. Sheets of a medium sized lymphoid cells with high proliferative activity, forming a 'starry sky' appearance, are noted. What cytogenic abnormality is most likely to be found?

[t\(11;14\)13%t\(14;18\)16%t\(8;14\)46%t\(9;22\)18%t\(11;18\)6%](#)

This patient has an immunodeficiency-associated Burkitt lymphoma.

## Burkitt's lymphoma

Burkitt's lymphoma is a high-grade B-cell neoplasm. There are two major forms:

- endemic (African) form: typically involves maxilla or mandible
- sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV

Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8;14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

### Microscopy findings

- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Management is with chemotherapy. This tends to produce a rapid response which may cause 'tumour lysis syndrome'. Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin\*) is often given before the chemotherapy to reduce the risk of this occurring. Complications of tumour lysis syndrome include:

- hyperkalaemia
- hyperphosphataemia
- hypocalcaemia
- hyperuricaemia

- acute renal failure

\*allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

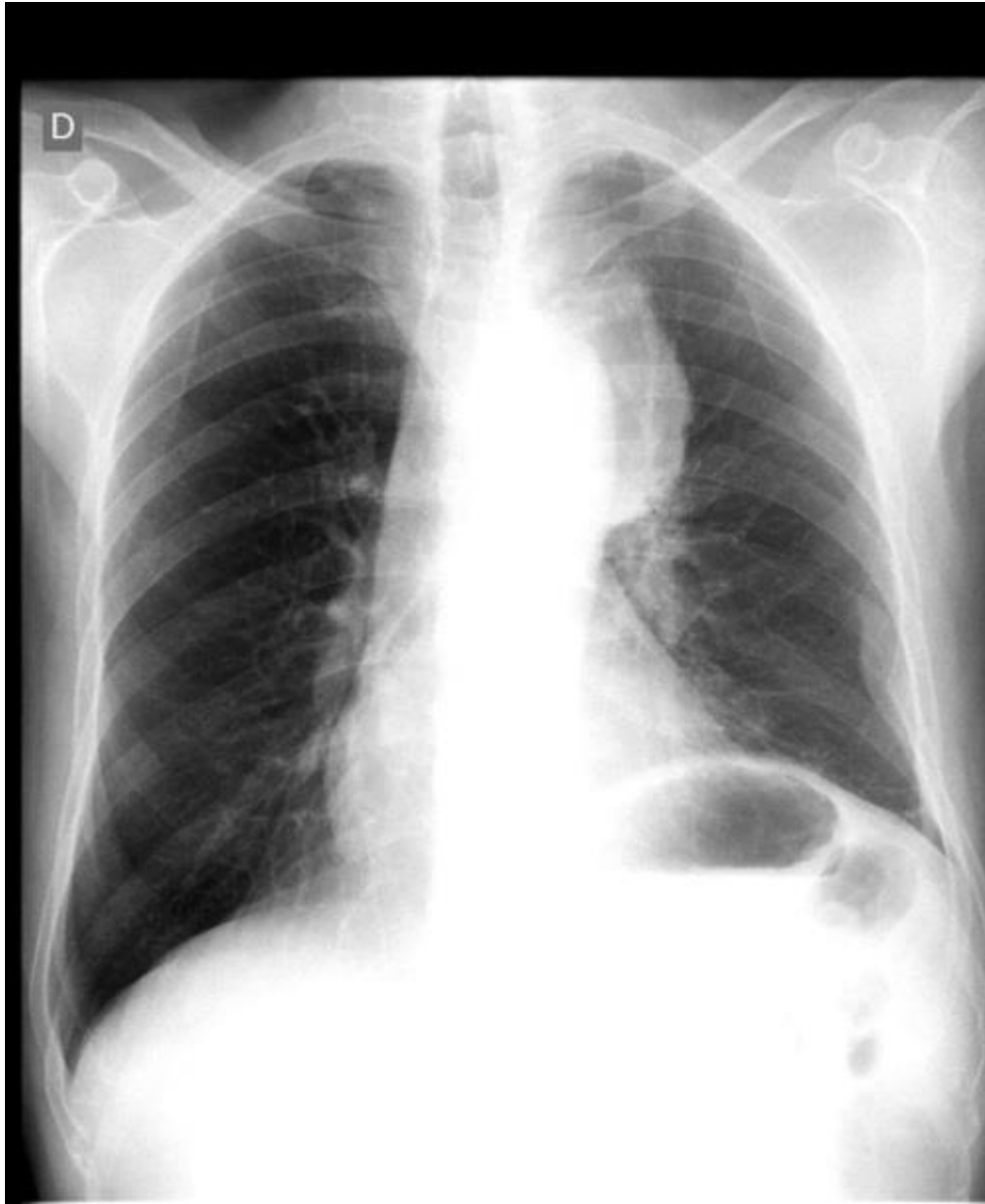
#### Question 7 of 91

A 70-year-old man is investigated for dysphagia and chest pain. These symptoms have been getting progressively worse for the past 3 months and have not responded to a trial of a proton pump inhibitor. There is no history of weight loss or anorexia.

On examination you note a left-sided partial ptosis. The patient also complains of double vision when you are assessing eye movements. Sustained upward gaze exacerbates his ptosis.

A chest x-ray is requested:





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What is the most likely diagnosis?

[Lung cancer](#)16%[Cardiac myxoma](#)6%[Tuberculosis](#)4%[Sarcoidosis](#)4%[Thymoma](#)70%

Mediastinal mass + symptoms of myasthenia = thymoma

The chest x-ray shows a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour. These findings are consistent with a thymoma.

The history is highly suggestive of myasthenia gravis which is seen in around a third of patients

with a thymoma. Note how the ptosis worsened with sustained upward gaze, a demonstration of fatigability.

## **Thymoma**

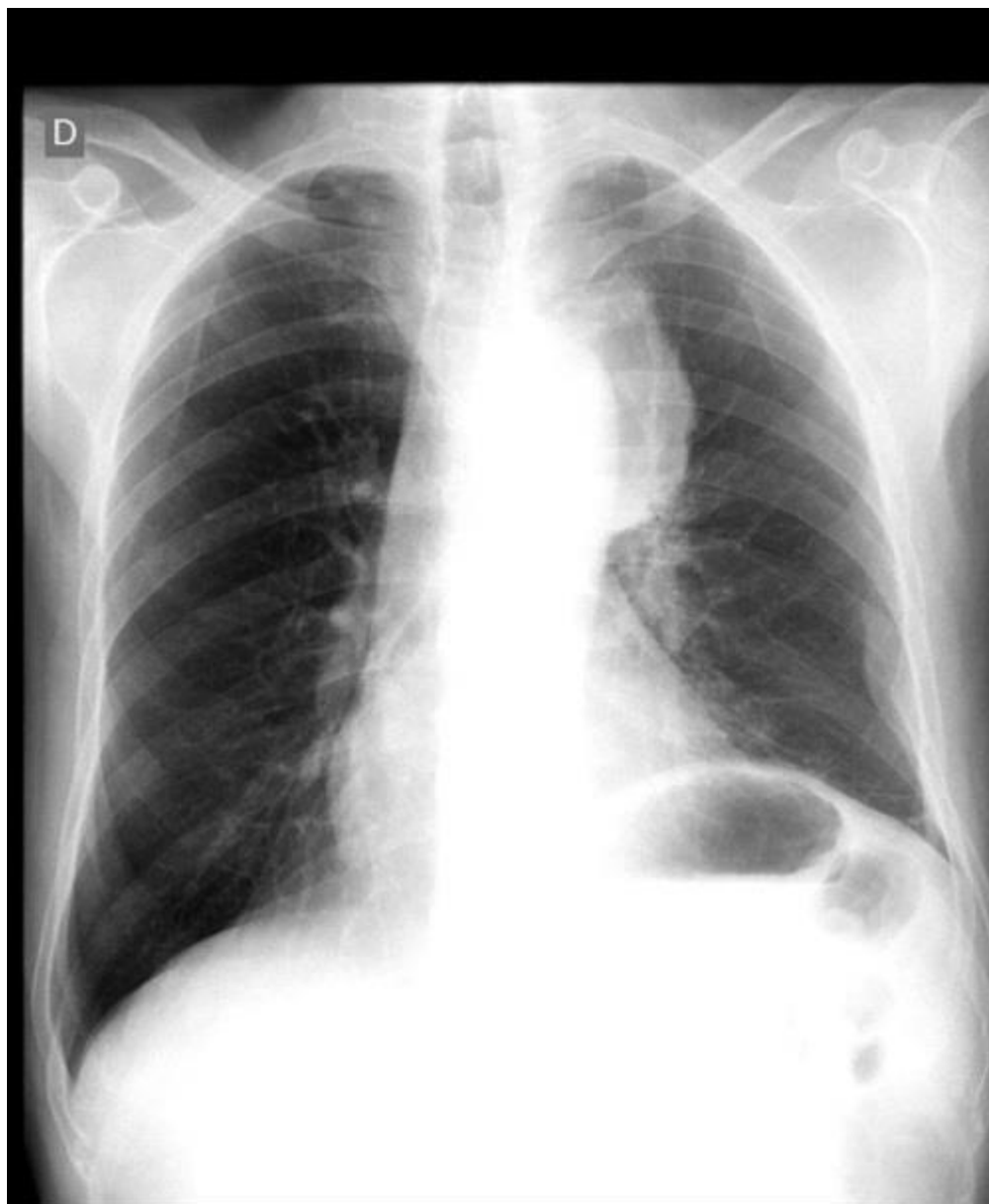
Thymomas are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

Associated with

- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also : SLE, SIADH

Causes of death

- compression of airway
- cardiac tamponade



© Image used on license from [Radiopaedia](#)

Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour.



© Image used on license from [Radiopaedia](#)

CT slice at the bifurcation of the main bronchus showing an invasive thymoma presenting as an anterior mediastinal mass

#### Question 8 of 91

An 85-year-old male is referred by the anaesthetic registrar after abnormal blood test results were noted during pre-assessment for an elective hip replacement. He is otherwise fit and well, independent with all activities of daily living and continues to drive. His past medical history includes diet controlled type 2 diabetes mellitus and hypertension. On examination, he is alert

and well, reports no discomfort, pain, or non-specific malaise. No skin bruises or conjunctival pallor are noted. You note a rubbery, non-tender and firm 3cm lymph node in the left cervical chain and non-tender splenomegaly at 8cm below the costal margin. His chest is clear and normal heart sounds are noted. His blood tests are as follows, with blood tests from his GP 6 months ago in brackets:

Hb 89 (95) g/l

Platelets 78 (76) \* 10<sup>9</sup>/l

WBC 67 (32) \* 10<sup>9</sup>/l

Blood film mature lymphocytes and smudge cells

What is the most appropriate treatment?

[Monitor and repeat blood count in 6 months39%Fludarabine, cyclophosphamide and rituximab treatment immediately44%Delayed chlorambucil treatment in 6 months8%Platelet transfusion4%Intravenous immunoglobulin5%](#)

This patient is on the cusp of requiring immediate treatment for chronic lymphocytic leukaemia. The latest guidelines are provided by the British Committee for Standards in Haematology (BCSH) 2012<sup>1</sup>, recommending immediate treatment to commence if the patient demonstrates signs of progressive marrow failure, massive or symptomatic splenomegaly greater than 6cm below the costal margin, massive or symptomatic nodes greater than 10cm in longest diameter, progressive lymphocytosis with doubling in 6 months, autoimmune thrombocytopaenia or anaemia, or significant constitutional symptoms within the previous 6 months. It is important to note that doubling of lymphocytosis is calculated only if the initial count is greater than 30 x 10<sup>9</sup>/l.

Asymptomatic patients not meeting these criteria do not benefit in long term survival when receiving immediate chlorambucil therapy versus delayed treatment<sup>2</sup>. Regular blood test monitoring is more appropriate for this group of patients. Be aware that despite increased white cell counts, the mature lymphocytes are non-functional and patients are hence at increased risk of infections. Intravenous immunoglobulin may be appropriate if the patient shows features of a significant infection. Similarly, significant progressive marrow failure, demonstrated by symptomatic anaemia or thrombocytopaenia may require replacement. In this case, the patient fits criteria for immediate treatment based on his lymphocytosis doubling time and splenomegaly.

1. British Committee for Standards in Haematology (BCSH) 2012

2. Chemotherapeutic options in chronic lymphocytic leukaemia: a meta-analysis of the randomised trials. CLL Trialists' Collaborative Group. J Natl Cancer Inst. 1999;91(10):861

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## Chronic lymphocytic leukaemia: management

### Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopenias e.g. ITP

### Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

### Question 2 of 83

A 36-year-old female was referred to the outpatient haematology clinic having been referred by her GP with a falling white cell count. Eight weeks ago she saw her own GP complaining of feeling continuously tired after a viral upper respiratory illness two weeks prior to the onset of her symptoms. She also complained of feeling generally unwell and of having intermittent pains in all her joints and muscles without swelling or stiffness. Her respiratory symptoms had fully resolved and she denied any night sweats or weight loss. Her GP organised a set of screening blood investigations which revealed a white cell count of  $2.6 \times 10^9$  g/dl (neutrophil count  $2.0 \times 10^9$  g/dl). This was repeated on two further occasions over the next four weeks revealing results of 2.2 and 1.9 respectively (neutrophil counts of  $1.5 \times 10^9$  g/dl and  $1.2 \times 10^9$  g/dl respectively). Her past medical history included hypothyroidism for which she was treated with levothyroxine 150mcg OD.

Examination at the clinic revealed the presence of a systemically well female. Her blood pressure was 118/74 mmHg, heart rate 82 bpm, respiratory rate 16/min and temperature 36.6°C. Examination of her cardiovascular system was unremarkable. Similarly, examination of her gastrointestinal system was unremarkable, with no organomegaly identified. No cervical, axillary or inguinal lymph nodes were palpable. Examination of her ENT system was unremarkable.

Initial investigations at the clinic revealed the following results:

Hb	122 g/l
WCC	$2.0 \times 10^9/l$
Neutrophils	$1.3 \times 10^9/l$
Lymphocytes	$0.6 \times 10^9/l$
Monocytes	$0.1 \times 10^9/l$
Platelets	$224 \times 10^9/l$
Blood film	neutropaenia
B12	224 (NR 160-900 ng/l)
ESR	15 mm/hr
CRP	9 mg/l
TSH	0.35 (NR 0.4-3.6mu/ml)
FT4	11.6 (NR 4.5-13.6 mcg/dl)
Monospot test	negative
CMV serology	negative

What is the single most appropriate management option?

[Organise bone marrow aspirate and biopsy26%](#)[Organise peripheral blood flow cytometry analysis17%](#)[Repeat full blood count in four weeks 40%](#)[Organise CT neck, thorax, abdomen and pelvis6%](#)[Organise blood cytogenetic analysis11%](#)

This is a very common scenario seen in the haematology outpatient clinic. This patient most probably has transient myelosuppression secondary to a viral infection with post viral fatigue and malaise. Although she is symptomatic, she is systemically well and there are no other red flag symptoms or signs including the presence of lymphadenopathy and splenomegaly. Her neutrophil count has been falling but it has remained above 1 and she is not febrile or septic. Her neutrophil count is beginning to improve (albeit very slowly) and therefore a repeat FBC would be justified to ensure that it does return to normal. If it remains low further investigation would be justified.

## Neutropaenia

### Causes

- viral
- drugs e.g. carbimazole, clozapine

- haematological malignancy
- aplastic anemia
- haemodialysis

#### Question 1 of 83

A 34 year old man is admitted under the medics from the emergency department with central abdominal pain and vomiting not responding to IV morphine. He had been seen by the surgeons earlier in the day as an acute abdomen, but the CT scan they did of his abdomen and pelvis revealed no abnormalities, and his bloods suggested no surgical cause of the abdominal pain.

You note that the patient has presented to the emergency department five times in the past two years with similar problems, and no cause has ever been found, with the patient being discharged one or two days later with analgesia.

On examination his abdomen is generally tender with evidence of voluntary guarding. On further examination you note that he has a rash on the back of his hands, neck and cheeks. This rash consists of several small fluid filled bullae.

His past medical history includes depression - for which he is taking citalopram, and one short psychiatric inpatient stay for an episode of psychosis.

What is the most likely diagnosis?

[Erythropoietic protoporphyria6% Porphyria cutanea tarda34% Hereditary coproporphyria18% Acute intermittent porphyria37% Congenital erythropoietic porphyria5%](#)

The porphyrias are a group of rare inborn errors of metabolism caused by abnormalities of enzymes involved in the biosynthesis of haem, resulting in overproduction of intermediate compounds called porphyrins.

Three patterns of symptoms occur clinically with porphyrias:

- 1) Neurovisceral - neuropathy, epilepsy, psychiatric disorders, abdominal, vomiting, constipation
- 2) Photosensitive - bullous eruption in sun exposed areas
- 3) Haemolytic

Neurovisceral only	Photosensitive only	Mixed
Acute intermittent porphyria	Porphyria cutanea tarda	Variegate porphyria
Aminolaevulinic acid dehydrogenase porphyria	Congenital erythropoietic porphyria	Hereditary coproporphyria
-	Erythropoietic protoporphyria	-

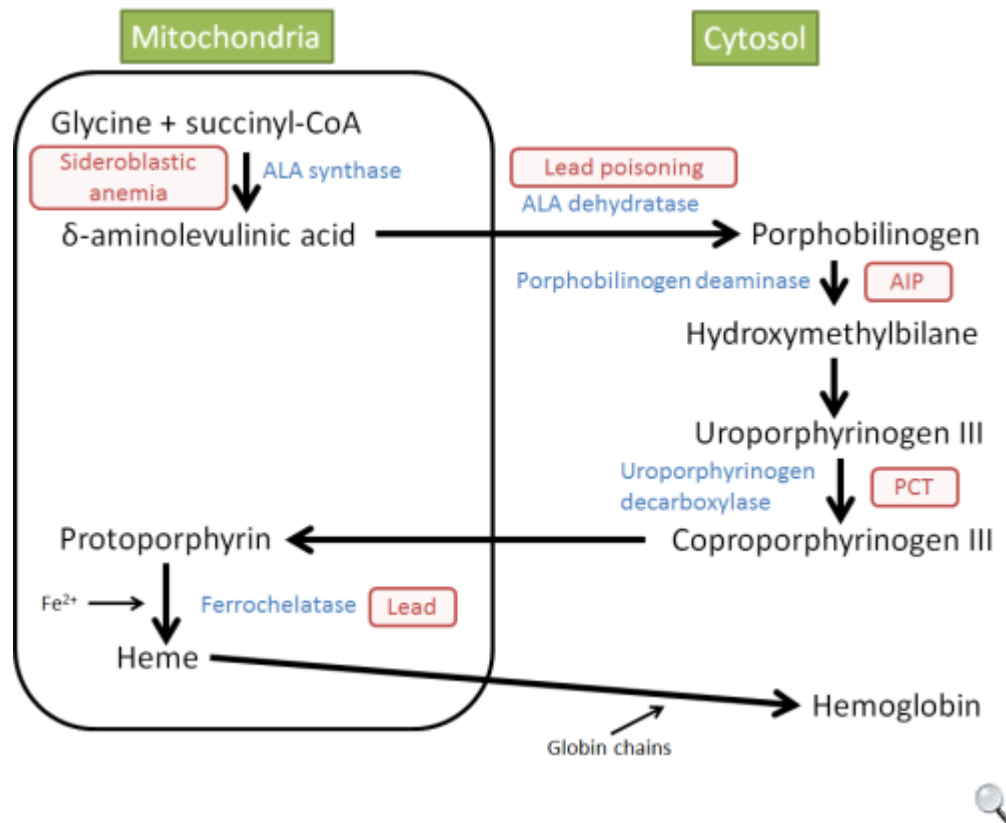
This patient has both photosensitive symptoms; his rash, and neurovisceral symptoms; abdominal pain and previous psychiatric history. The only mixed presentation porphyria given as a possible answer is hereditary coproporphyria, hence it is the correct answer.



## Porphyrias

### Overview

- abnormality in enzymes responsible for the biosynthesis of haem
- results in overproduction of intermediate compounds (porphyrins)
- may be acute or non-acute



### Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms

- hypertension and tachycardia common
- urine turns deep red on standing

#### Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

#### Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

#### Question 3 of 83

A 35-year-old woman who was diagnosed with hereditary angioedema is about to undergo an elective meniscal repair for her left knee. She has been well otherwise with no recent changes to her health or medications. Which is the drug of choice for prophylaxis for her hereditary angioedema prior to her procedure?

[Prednisolone10%Hydrocortisone19%Conestat alfa20%Tranexamic acid27%Icatibant24%](#)

The best answer here is tranexamic acid.

In hereditary angioedema, the relevant medications can be used as follows:

A C1-esterase inhibitor can be used for short-term prophylaxis before procedures or to terminate acute attacks of hereditary angioedema. Conestat alfa and icatibant are licensed for the treatment of acute attacks of hereditary angioedema in adults with C1-esterase inhibitor deficiency.

Tranexamic acid and danazol are used for short-term and long-term prophylaxis.

There is no role of glucocorticoids in this case.

## Hereditary angioedema

Hereditary angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in oedema of tissues.

### Investigation

- C1-INH level is low during an attack
- low C2 and C4 levels are seen, even between attacks. Serum C4 is the most reliable and widely used screening tool

### Symptoms

- attacks may be preceded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)
- urticaria is not usually a feature

### Management

- acute: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help

### Question 1 of 80

A 61-year-old woman comes for review. Around one year ago she finished a 6 month course of warfarin after being diagnosed with an unprovoked, proximal deep vein thrombosis. For the past few weeks she has been experiencing 'heaviness' and 'aching' in the the same leg. This is associated with an itch and some swelling, although this seems to go down each night. Past medical history of note includes osteoarthritis and type 2 diabetes mellitus.

On examination prominent varicose veins are seen on the affected leg with some brown discolouration of the skin above the medial malleolus. There is no difference in the

circumference of the calves. Her temperature is 36.9°C, pulse 78/min and blood pressure 108/82 mmHg. What is the most likely diagnosis?

[Recurrence of deep vein thrombosis7%](#)[Post-thrombotic syndrome63%](#)[Cellulitis6%](#)[Ruptured Baker's cyst6%](#)[Necrobiosis lipoidica18%](#)

The slowly progressive symptoms of pruritus and pain accompanied by the examination findings are strongly suggestive of post-thrombotic syndrome.

### **Post-thrombotic syndrome**

It is increasingly recognised that patients may develop complications following a DVT. Venous outflow obstruction and venous insufficiency result in chronic venous hypertension. The resulting clinical syndrome is known as post-thrombotic syndrome. The following features maybe seen:

- painful, heavy calves
- pruritus
- swelling
- varicose veins
- venous ulceration

Compression stockings have in the past been offered to patients with deep vein thrombosis to help reduce the risk of post-thrombotic syndrome.

However, Clinical Knowledge Summaries now state the following:

*Do not offer elastic graduated compression stockings to prevent post-thrombotic syndrome or VTE recurrence after a proximal DVT. This recommendation does not cover the use of elastic stockings for the management of leg symptoms after DVT.*

However, once post-thrombotic syndrome has developed compression stockings are a recommended treatment. Other recommendations including keeping the leg elevated.

A 68-year-old gentleman with known chronic lymphocytic leukaemia (CLL) is reviewed in the Haematology Clinic.

He is normally an active gentleman who enjoys playing golf 3 times per week, but he complains that he has been feeling increasingly fatigued since his last appointment 6 months previously. He states that he has not been able to play golf for several weeks and his wife tells you that he has started napping during the afternoons. His past medical history is otherwise unremarkable and he takes no regular medications.

Examination reveals a tired gentleman with marked axillary and inguinal lymphadenopathy. His abdomen is soft with mild upper abdominal tenderness. A liver edge is palpable 3cm below the costal margin and his spleen is markedly enlarged.

His full blood count today is as follows:

Hb	114 g/l
Platelets	$173 \times 10^9/l$
WBC	$30.4 \times 10^9/l$
Neutrophils	$5.8 \times 10^9/l$
Lymphocytes	$23.1 \times 10^9/l$

His lymphocyte count 2 months ago was  $15.3 \times 10^9/l$  and a decision to start the patient on fludarabine, cyclophosphamide, and rituximab (FCR) chemotherapy is taken.

Given the proposed treatment strategy, which of the following prophylactic medications is it most important to start?

[Co-trimoxazole54% Aciclovir12% Entecavir6% Fluconazole10% Penicillin V16%](#)

Fludarabine is a purine analogue that prevents DNA synthesis through the inhibition of ribonucleotide reductase and DNA polymerase. It is associated with profound lymphopenia, and significantly increases the risk of opportunistic infections. Patients treated with fludarabine are at particular risk of morbidity and mortality secondary to pneumocystis pneumonia. It is essential that these patients receive regular prophylactic co-trimoxazole.

Purine analogues can lead to herpes simplex, herpes zoster, and cytomegalovirus reactivation and aciclovir is often given as prophylaxis against this. Fluconazole is also frequently given as fungal prophylaxis.

Entecavir is given to patients who are hepatitis B surface antigen (HBsAg) positive.

Penicillin V is given to patients with asplenia and is not routinely used in this setting.

Pneumocystis pneumonia is the most severe complication described. Co-trimoxazole is, therefore, the most essential of the medications listed above.

## Chronic lymphocytic leukaemia: management

### Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopenias e.g. ITP

### Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

### Question 1 of 76

A patient has been admitted with left lower limb deep vein thrombosis. He was diagnosed by the FY1 who has efficiently started him on warfarin.

Two days after initiation you are asked to see this gentleman who has developed skin necrosis over his right thigh.

What is the most likely cause of his skin necrosis?

[Antiphospholipid syndrome5%](#)[Heparin induced thrombocytopenia \(HIT\) type II8%](#)[Excessive serum Antithrombin III8%](#)[Acquired haemophilia5%](#)[Protein C deficiency74%](#)

Answer: Protein C deficiency.

Warfarin induced skin necrosis is rare but very severe.

Be reminded that warfarin inhibits production of the vitamin K dependent coagulation factors

including factors II, VII, IX and X but also the natural anticoagulants, proteins C and S. The first factors affected by warfarin are the anticoagulants, making warfarin temporarily pro-thrombotic during induction, in its initial few days of use and that is why it is advised to start heparin concurrently with Warfarin.

Various theories have been postulated as to the cause of this problem one of which is a background of congenital or acquired protein C, S or Antithrombin III deficiency.

Antithrombotic therapy for atrial fibrillation BMJ 2002; 325 doi:  
<http://dx.doi.org/10.1136/bmj.325.7371.1022> (Published 02 November 2002)

Cite this as: BMJ 2002;325:1022 <http://www.bmj.com/rapid-response/2011/10/29/warfarin-induced-skin-necrosis>

Coumadin-Induced Skin Necrosis Janice M. Beitz, PhD, RN, CS, CNOR, CWOCN  
<http://www.medscape.com/viewarticle/4431264>

## **Protein C deficiency**

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis

### **Features**

- venous thromboembolism
- skin necrosis following the commencement of warfarin: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis

### **Question 2 of 76**

A 30-year-old previously fit and well gentleman is injured following a road traffic accident after being thrown off his motorcycle. He was blue-lighted to the emergency department, where he was found to have multiple, profusely bleeding, lacerations of his extremities.

He was transfused 2 units of cross-matched blood, with no reactions detected in blood bank. Ten

minutes after the transfusion, the patient developed severe urticaria.

Which of the following syndromes would contribute to the patient's picture?

[Adenosine deaminase deficiency23% Ataxia telangiectasia6% DiGeorge syndrome8% Selective IgA deficiency47% Wiskott-Aldrich syndrome15%](#)

The majority of selective IgA deficiency patients are asymptomatic; with about 5% suffering from recurrent respiratory tract infections. The condition becomes clinically significant when blood transfusion is required, as there is the potential for anaphylaxis to occur on exposure to IgA containing blood products.

Although rare, anaphylaxis can happen from the first transfusion if the patient has been previously exposed to IgA i.e. in consumed animal meat products. If ever the patient needs a future blood transfusion, the transfused blood must be IgA free.

## Primary immunodeficiency

Primary immunodeficiency disorders may be classified according to which component of the immune system they affect.

### Neutrophil disorders

Disorder	Underlying defect	Notes
Chronic granulomatous disease	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. <i>Staphylococcus aureus</i> and fungi (e.g. <i>Aspergillus</i> ) Negative nitroblue-tetrazolium test Abnormal dihydrorhodamine flow cytometry test
Chediak-Higashi syndrome	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets
Leukocyte adhesion deficiency	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection



## B-cell disorders

Disorder	Underlying defect	Notes
Common variable immunodeficiency	Many varying causes	Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphoma
Bruton's (x-linked) congenital agammaglobulinaemia	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen Absence of B-cells with reduced immunoglobulins of all classes Most common primary antibody deficiency. Recurrent sinus and respiratory infections
Selective immunoglobulin A deficiency	Maturation defect in B cells	Associated with coeliac disease and may cause false negative coeliac antibody screen  Severe reactions to blood transfusions may occur (anti-IgA antibodies → anaphylaxis)

## T-cell disorders

Disorder	Underlying defect	Notes
DiGeorge syndrome	22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate

## Combined B- and T-cell disorders

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles Stem cell transplantation may be successful
Ataxia telangiectasia	Defect in DNA repair enzymes	Autosomal recessive. Features include cerebellar ataxia, telangiectasia (spider angiomas), recurrent chest infections and 10% risk of developing

Disorder	Underlying defect	Notes
Wiskott-Aldrich syndrome	Defect in WAS gene	malignancy, lymphoma or leukaemia X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy

### Question 3 of 76

A 45 year old man is admitted from a local park. On arrival he is in respiratory distress with a ventilatory rate of 34 breaths per minute and a peripheral oxygen saturation of 89% on 15L/min oxygen via non-rebreathe mask. He is grey and sweaty with central cyanosis. Heart rate is 122bpm and blood pressure is 94/66mmHg. Examination of the chest discloses a normal cardiorespiratory examination and there is no clinical indication of heart failure. A chest xray shows no acute pathological lesion but background emphysematous changes and an ECG shows only sinus tachycardia with a corrected QT interval approaching the upper limit of normal with no ischaemic lesions.

An arterial blood gas taken on 15L/min oxygen shows:

pH 7.17 HCO<sub>3</sub><sup>-</sup> 13.4 Glucose 6.9 mmol/l MetHb 35%  
pO<sub>2</sub> 10.9 Base excess -5.8 Potassium 5.5 mmol/l COHb 8%  
pCO<sub>2</sub> 6.7 Lactate 4.1 mmol/l

He is beginning to show signs of tiring and confusion and his GCS has fallen to 13/15 (E3V4M6) but he tells you he has been inhaling Liquid Gold (an alkyl nitrite).

Which of the following interventions is most appropriate in this patients immediate management?

[Continuous positive airways pressure ventilation \(CPAP\) pending transfer to a hyperbaric chamber](#)  
[18% Reduce inspired oxygen concentration and controlled oxygen therapy via Venturi valve](#)  
[7% 75mg 1% methylthioninium chloride solution IV over 5 minutes](#)  
[47% 300mg 3% sodium nitrite solution IV over 10 minutes](#)  
[12% 50ml 8.4% sodium bicarbonate solution IV over 20 minutes](#)  
[16%](#)

Poppers (alkyl nitrites) may rarely cause methaemoglobinaemia which is treated first line with methylthioninium chloride solution (methylene blue)

The arterial blood gas in the above clinical description shows a mixed respiratory and metabolic acidosis with a relative hypoxia despite the inspired fraction of oxygen. However, the significant

abnormality is the fraction of methaemoglobin on the gas at over 30% which is significantly elevated. The carboxyhaemoglobin level is slightly raised at 8% but levels such as this may be seen in smokers and are not necessarily pathological. In this case, the diagnosis is of acute methaemoglobinaemia which is a rare but potentially fatal consequence of inhalation of poppers (alkyl nitrites).

Poppers are a clear or yellowish, sweet smelling volatile liquid which is inhaled as a recreational drug of abuse which yields euphoric and anxiolytic effects. It also is a vasodilator and is sometimes used as an adjunct in sexual acts, and previously was a treatment for angina pectoris. However, in some patients, particularly susceptible individuals such as those with sickle cell traits or a G6PD deficiency, inhalation of poppers may rapidly oxidise ferrous iron ions in haemoglobin to their ferric ( $\text{Fe}^{3+}$ ) states creating methaemoglobinaemia (MetHb). MetHb binds oxygen more avidly than haemoglobin and causes a shift in the dissociation curve to the left meaning that oxygen is not liberated in the tissues causing a cellular hypoxia. This manifests in a clinical cyanosis and often a deathly grey pallor to the patient. Oxygen saturations may not be as shocking as the patient appears since many pulse oximeters cannot distinguish between oxyhaemoglobin and methaemoglobin well. However, supplemental oxygen will not improve recorded values (although it should still be given). An impairment in gas exchange is often seen in acute methaemoglobinaemia with raised tensions of  $\text{CO}_2$  and low tension of  $\text{O}_2$  and consequent respiratory acidosis. An additional metabolic acidosis occurs due to cellular anoxic respiration. In smokers, this condition may be mistaken for a type 2 respiratory failure due to chronic obstructive lung disease. The methaemoglobin count and low bicarbonate make this unlikely and reducing the inspired oxygen is likely to worsen the situation. CPAP may be tried but will not reverse the underlying problem and hyperbaric oxygen is helpful only in situations of high carboxyhaemoglobin, such as carbon monoxide poisoning, which is not the case here.

The first line treatment for methaemoglobinaemia is administration of methylthioninium chloride, also known as methylene blue, which reduces the ferric ions back to their ferrous states rapidly. Several administrations may be required, especially in high concentrations of MetHb. Sodium nitrite is a recognised treatment for cyanide poisoning. It actually causes methaemoglobinaemia since cyanide ions are cleared more rapidly when complexed with MetHb. Administration of sodium nitrite is not indicated in this vignette and will make the situation worse. Sodium bicarbonate may well be indicated in this patient due to the profound acidosis but it is not the most pressing concern. Rectification of the oxygen carrying capacity of the blood may improve the acid-base balance without the need for bicarbonate, and hypoxia is likely to kill the patient more quickly than acidosis with a normal potassium. Remember that 8.4% bicarbonate solution, if given, should ideally be infused through a central vein since it is extremely caustic.

## **Methaemoglobinaemia**

Methaemoglobinaemia describes haemoglobin which has been oxidised from  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ . This

is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as Fe<sup>3+</sup> cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

#### Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

#### Acquired causes

- drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

#### Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal pO<sub>2</sub> but decreased oxygen saturation

#### Management

- NADH - methaemoglobinaemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

#### Question 1 of 73

You are working in haematology. A 72-year-old man has been referred to you by the general surgeons. He recently had a CT scan for weight loss and a two month change in bowel habit. This showed no lesions within the bowel but did demonstrate some mesenteric lymphadenopathy. The largest lymph node was 4 cm in diameter. He is otherwise well and has a background of hypertension and diet controlled diabetes. He subsequently underwent a CT guided biopsy (histology report below).

The lymph node biopsied lacks a mantle zone and is made up of a predominant population of centrocytes with few tangible body macrophages. Immunohistochemistry confirms strong positivity for CD20 as well as CD70a, CD10, BCL2 and BCL6. The proliferation index (Ki-67)

is low, no more than 20%.

What is the most likely diagnosis?

[Nodular sclerosing lymphoma17%](#)[Lymphoplasmacytic lymphoma13%](#)[Follicular lymphoma29%](#)[Adenocarcinoma of the large bowel5%](#)[Diffuse large B cell lymphoma37%](#)

The correct answer here can be worked out based on the Ki-67 index. This is the proliferation index and is a marker (antigen) of the cancer cells metabolic rate. In high grade lymphomas such as diffuse large B cell lymphoma the Ki-67 will be high (>45%) therefore answer 5 is wrong. In low grade lymphomas such as follicular lymphoma the Ki-67 is low (<40%).

Follicular lymphoma (a form of non Hodgkin's lymphoma) often presents as incidentally found enlarged lymph nodes and may present without the B symptoms often seen in Hodgkin's lymphoma. It can undergo a transformation at any stage into a high grade lymphoma.

Answer 1 is wrong because as it is a form of Hodgkin's lymphoma the histology report would have mentioned the presence of reed-sternberg cells. Answer 2 is Waldenström's macroglobulinemia and presents with an IgM gammopathy. Answer 4 is wrong because an adenocarcinoma of the large bowel would have most likely been seen on a CT scan.

## **Non-Hodgkin's lymphoma**

### Features

- median age = 55-60 years
- painless widespread lymphadenopathy, hepatosplenomegaly
- raised LDH, paraproteinaemia, AIHA

### Management

- rituximab, anti-CD20 monoclonal antibody
- stem cell transplantation

A 67-year-old gentleman presents to the emergency department following a fall. He tripped on the carpet and landed on his back. Following this he has been complaining of lower back pain, but this pain was present prior to his fall and only slightly worsened with the accident. He undergoes a CT scan which unfortunately demonstrates lytic lesions in his lumbar vertebrae. He is suspected of having multiple myeloma. He undergoes blood and urine tests which unfortunately raises further suspicion of the diagnosis. He is due to undergo a bone marrow biopsy. What investigation prior to the biopsy can give prognostic information?

[Serum immunofixation4%B2 microglobulin73%Serum corrected calcium8%Protein electrophoresis9%Urine electrophoresis6%](#)

The correct answer is B2 microglobulin. This is a patient who has unfortunately found to have multiple myeloma and is awaiting further investigation to obtain histology. B2 microglobulin elevation and fall in albumin are associated with a poor prognosis. Serum immunofixation and electrophoresis studies are useful diagnostic tools but are not as useful in terms of prognosis.

Source:

'Myeloma: diagnosis and management.' NICE guideline [NG35]. The National Institute for Health and Care Excellence, February 2016.

## Myeloma: prognosis

B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Low levels of albumin are also associated with a poor prognosis

### International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
III	B2 microglobulin > 5.5 mg/l	29

### Question 3 of 73

A 23 year old male of Nigerian descent is referred from the ED with acute shortness of breath associated with fever and dry cough. His shortness of breath has limited him to an exercise

tolerance of around 10 yards. He also complains of excruciating right sided chest pain. He is known to have sickle cell anaemia and has had no admissions to the hospital in the last 3 years.

#### Observations

- heart rate 94bpm regular
- blood pressure 112/74 mmHg
- temperature 38.3
- respiratory rate 22
- urine output under 30ml/hr
- oxygen saturations 93% on room air

#### Examination

- respiratory system shallow breathing, bronchial breath sounds with crepitations to right base

#### Blood results:

Hb 7.7 g/dl

Platelets  $200 \times 10^9/l$

WBC  $13.2 \times 10^9/l$

Bilirubin 36  $\mu\text{mol/l}$

Urea 8.2 mmol/l

Creatinine 146  $\mu\text{mol/l}$

What is the most important initial steps in management?

[Oxygen, IV fluids, antibiotics and analgesia67%2 unit blood transfusion and analgesia6%Oxygen and analgesia only9%Antibiotics and IV fluid only5%Plasmapheresis and analgesia13%](#)

It is important to recognise and treat sickle cell crises (as detailed above) as a matter of urgency. This condition can be quickly fatal. This patient should be treated as per sepsis guidelines. It is crucial to adequately control the pain in this patient cohort as not being able to inhale deeply due to pain will only serve to worsen the lung damage. Early assessment for the involvement of the critical care team is required as acute respiratory distress syndrome is a real possibility. Oxygen saturation levels should be maintained above 95% in a patient where a normal steady state level is not known. Management of this and the haemoglobin level should be specific for the patient

and compared to past levels. The question states that the patient has had no admissions to the hospital in the last 3 years and as such the aim should be to keep oxygen saturations above 95%.

## **Sickle-cell crises**

Sickle cell anaemia is characterised by periods of good health with intervening crises

Four main types of crises are recognised:

- thrombotic, 'painful crises'
- sequestration
- aplastic
- haemolytic

### Thrombotic crises

- also known as painful crises or vaso-occlusive crises
- precipitated by infection, dehydration, deoxygenation
- infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain)

### Sequestration crises

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO<sub>2</sub> - the most common cause of death after childhood

### Aplastic crises

- caused by infection with parvovirus
- sudden fall in haemoglobin

### Haemolytic crises

- rare
- fall in haemoglobin due an increased rate of haemolysis



Question 4 of 73

You are called to see a 55-year-old gentleman who is having a blood transfusion for symptomatic anaemia secondary to colon cancer. The nurses have been doing regular observations as documented below.

10am: Baseline observations prior to blood transfusion

Respiratory rate 20 breaths/min  
Saturations 96% on air  
Temperature 37.5 °c  
Blood pressure 145/78 mmHg  
Heart rate 74 beats/min

10:15 am: repeat observations after 15 mins of transfusion

Respiratory rate 19 breaths/min  
Saturations 97% on air  
Temperature 38.2 °c  
Blood pressure 150/80 mmHg  
Heart rate 72 beats/min

The nurses have already stopped the blood transfusion by the time you arrive to see the patient. On questioning the patient he feels well with no complaints of pain, itch or rashes. On examination his heart sounds are pure and chest is clear. He has no previous documented reactions to blood transfusions although the patient informs you he is allergic to penicillin. What instructions do you give the nurses?

[Take blood cultures and commence antibiotics4%Dispose of the remaining blood in the bag7%Restart the blood transfusion after giving the patient paracetamol58%Take blood cultures, repeat chest x ray and perform urinalysis6%Restart the blood transfusion an hour after giving the patient paracetamol24%](#)

Blood transfusion reaction are common and can be serious. This patient is well and has no clinical evidence of haemodynamic compromise. He has an isolated pyrexia which is likely to be secondary to commencement of the blood transfusion. After confirming this his blood transfusion should be restarted as soon as possible and paracetamol given for symptomatic relief. Disposal of the blood should be considered if a serious adverse reaction occurs. Septic screen and antibiotics should be considered if any underlying infection is suspected. Blood transfusion should be completed within 4 hours and waiting an hour prior to restarting is a waste of valuable time.

## **Blood product transfusion complications**

### Complications

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, vCJD
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

### Immediate haemolytic reaction

- e.g. ABO mismatch
- massive intravascular haemolysis

### Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions

### Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

### Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
  - from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
  - from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
  - from 2004 onward, recipients of blood components have been excluded from donating blood

### Question 5 of 73

A 32 year-old man presents to the neurology clinic with burning pains in both feet, which has progressed over the last year.

His past medical history includes hepatitis C, and last year he was commenced on treatment with pegylated interferon and ribavirin.

On examination, power is normal throughout. Reflexes are present normally in the arms but only with reinforcement in the knees, and absent in the ankles. Sensation to pin-prick, joint position, and vibration is absent up to the knees.

Nerve conduction studies show reduction in the amplitude of lower limb sensory action potentials, in a length-dependent fashion. Conduction velocities are relatively preserved. Motor studies are normal.

What is the most likely cause of this mans pain?

[Diabetic small-fibre neuropathy](#)7%[Fabrys disease](#)6%[Drug-induced peripheral neuropathy](#)30%[Cryoglobulinaemic peripheral neuropathy](#)47%[Chronic inflammatory demyelinating polyradiculoneuropathy \(CIDP\)](#)10%

Cryoglobulinaemia is the presence of circulating proteins which precipitate in the cold. It is commonly associated with hepatitis C infection. Through a variety of mechanisms, cryoglobulins cause a small-vessel vasculitis which may result in an axonal peripheral neuropathy. This may be sensorimotor, or purely sensory.

Small-fibre neuropathy typically presents with pain and loss of temperature sensation, with relative preservation of other sensory modalities and muscle strength. This form of neuropathy is not detectable on conventional nerve conduction studies, which can only investigate large fibres. Diabetes is a common cause and should be excluded in any patient with a painful peripheral neuropathy.

Fabrys disease is an X-linked lysosomal storage disorder which causes a painful peripheral neuropathy, due to deposition of glycosphingolipids within small sensory fibres. Nerve conduction studies are typically normal as large fibres are unaffected.

Drugs such as metronidazole, isoniazid, and cytotoxic chemotherapy agents are common causes of peripheral neuropathy. However, the drugs this man is taking are not strongly associated with neuropathy.

CIDP typically presents with prominent motor involvement, often affecting proximal as well as distal muscles. Sensory involvement is common, often affecting joint position and vibration sense, which are mediated by large myelinated fibres. On nerve conduction studies the typical

finding is conduction slowing reflecting demyelination, rather than reduced amplitudes which suggest axonal loss.

## **Cryoglobulinaemia**

Immunoglobulins which undergo reversible precipitation at 4 deg C, dissolve when warmed to 37 deg C. One-third of cases are idiopathic

Three types

- type I (25%): monoclonal
- type II (25%): mixed monoclonal and polyclonal: usually with rheumatoid factor (RF)
- type III (50%): polyclonal: usually with RF

Type I

- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenstrom macroglobulinaemia

Type II

- mixed monoclonal and polyclonal: usually with RF
- associations: hepatitis C, RA, Sjogren's, lymphoma

Type III

- polyclonal: usually with RF
- associations: rheumatoid arthritis, Sjogren's

Symptoms (if present in high concentrations)

- Raynaud's only seen in type I
- cutaneous: vascular purpura, distal ulceration, ulceration
- arthralgia
- renal involvement (diffuse glomerulonephritis)

## Tests

- low complement (esp. C4)
- high ESR

## Treatment

- immunosuppression
- plasmapheresis

### Question 1 of 68

A 70 year-old woman presents with severe back pain which has been worsening over the last month. Prior to this she has never suffered from back pain. She has been lethargic, and her husband notes some intermittent confusion. A systemic enquiry reveals long standing exertional breathlessness, and constipation. She has no other bowel or bladder disturbance.

Her background includes chronic obstructive pulmonary disease, which is managed by her GP. She gave up smoking two years ago. Her well woman check up 12 months ago was entirely normal, aside from a slightly raised cholesterol which is being management with diet.

On examination, she has a normal gait. There is some mild tenderness over L3/L4 vertebra with no lower limb neurological deficit. Cardiorespiratory examination reveals an ejection systolic murmur, with a normal second heart sound.

Hb	90 g/l	Na <sup>+</sup>	135 mmol/l	Bilirubin	5 µmol/l
Platelets	200 * 10 <sup>9</sup> /l	K <sup>+</sup>	5.5 mmol/l	ALP	101 u/l
WBC	10 * 10 <sup>9</sup> /l	Urea	15 mmol/l	ALT	40 u/l
Neuts	8 * 10 <sup>9</sup> /l	Creatinine	230 µmol/l	corrected calcium	2.7 u/l
ESR	40 mm/hr				

What is the most likely diagnosis?

[Multiple myeloma78% Monoclonal gammopathy of undetermined significance6% Non-Hodgkin's, lymphoma3% Paget's disease6% Renal cell carcinoma with spinal metastases7%](#)

Multiple myeloma is malignant proliferation of plasma cells, producing a monoclonal protein detected in blood and/or urine; this causes organ or tissue damage. The median age of presentation is 70 years old.

Presenting clinical features include symptoms of:

- Impaired renal function- from light chain deposition from plasma cells, other causes include amyloid deposition, dehydration, hypercalcaemia, hyperviscosity, and nephrotoxic drugs
- Anaemia
- Hypercalcaemia- myeloma cells cause an increased production of osteoclast activating factors and cytokines that inhibit osteoblast differentiation
- Recurrent infections- decreased humoral immunity
- Hyperviscosity symptoms (headaches, epistaxis, blurred vision, and confusion)- high paraprotein levels
- Bone pain

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic condition thought to precede multiple myeloma.

### **Myeloma: features**

Multiple myeloma is a neoplasm of the bone marrow plasma cells. The peak incidence is patients aged 60-70 years.

#### **Clinical features**

- bone disease: bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- lethargy
- infection
- hypercalcaemia (see below)
- renal failure
- other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

#### **Investigations**

- monoclonal proteins (usually IgG or IgA) in the serum and urine (Bence Jones proteins)
- increased plasma cells in the bone marrow
- historically a skeletal survey has been done to look for bone lesions. However, whole-body MRI is increasingly used and is now recommended in the 2016 NICE guidelines

The diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

#### Major criteria

- Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
- 30% plasma cells in a bone marrow sample
- Elevated levels of M protein in the blood or urine

#### Minor criteria

- 10% to 30% plasma cells in a bone marrow sample.
- Minor elevations in the level of M protein in the blood or urine.
- Osteolytic lesions (as demonstrated on imaging studies).
- Low levels of antibodies (not produced by the cancer cells) in the blood.

#### Hypercalcaemia in myeloma

- primary factor: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels

#### Question 2 of 68

A 62-year-old woman presents to the haematology clinic. She has had lower back pain, which has been progressive in nature. She has also been noted to develop unexplained anaemia. Her initial protein electrophoresis and serum-free light chain assays raised suspicion of multiple myeloma. She has a past medical history of transient ischaemic attacks and hypertension. She takes clopidogrel, amlodipine and ramipril. What imaging should be offered to further assess her?

[Lumbosacral X-rays11% Skeletal survey50% Bone marrow ultrasound3% Whole body MRI25% PET scan11%](#)

The correct answer is whole body MRI. NICE advises that all patients suspected to have a diagnosis of myeloma should be offered whole body MRI as first-line imaging, and only consider whole body CT if the patient declines MRI or is unable to have it. Skeletal survey should only be considered if CT and MRI are both not possible. Fluorodeoxyglucose positron emission tomography CT (FDG PET CT) can be considered once a diagnosis is confirmed.

Source:

'Myeloma: diagnosis and management.' NICE guideline [NG35]. The National Institute for Health and Care Excellence, February 2016.

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- bone disease: bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- lethargy
- infection
- hypercalcaemia (see below)
- renal failure
- other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

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### Question 5 of 68

A 32 year old patient presents the acute medical unit with 6 hour history of worsening chest pain. Otherwise he mentions that he has been feeling generally more tired than normal recently, is more breathless than usual and has noticed some dark discolouration of his urine, especially in the mornings. He has a past medical history of deep vein thrombosis (DVT) in his left leg for which he had 6 months of warfarin therapy 2 years ago.

An immediate ECG is performed with shows anterior ST depression and T wave inversion.

CXR: nil acute

Blood tests:

Troponin I 1.02 µg/L (elevated)

Hb 102 g/l

Plt 101 x10<sup>9</sup>/l

WCC 5.7 x10<sup>9</sup>/l

Na<sup>+</sup> 136 mmol/l

K<sup>+</sup> 5.0 mmol/l

Urea 8 mmol/l

Creatinine 79 µmol/l

The patient is taken to the cath lab due to his cardiac sounding chest pain with ECG and cardiac enzyme abnormalities. The coronary angiogram shows a thrombosis of the left anterior

descending artery, which is aspirated during the procedure. No significant atherosclerotic plaque formation or stenosis of the coronary arteries is identified.

Given this gentleman's presentation, which of the following investigations would be most useful to do next?

[Anti cardiolipin antibodies 9% Acid haemolysis test 47% Antiphospholipid antibodies 15% Factor V leiden levels 17% Coombs' test 12%](#)

This gentleman has paroxysmal nocturnal haemoglobinuria (PNH). He had arterial thrombosis (he has had a non-ST elevation myocardial infarction given his ECG changes and troponin rise - this has been identified as being caused by a thrombus in the left anterior descending artery on the coronary angiogram. During angioplasty - the operator will firstly opt to diagnose the problem by cannulating the left main stem coronary artery. Once they he/she identifies the lesion, they can opt to perform intervention in the way of:

- Balloon angioplasty
- Placement of a drug eluting stent
- Thrombus aspiration
- A combination of the above

He also had venous thrombosis (the classical presentation for 50% of cases) coupled with anaemia, anaemic symptoms, and discolouration of the urine which is noted more prominently in the morning when the urine is more concentrated. The key screening investigation in diagnosing PNH is Ham's acid haemolysis test - placing the blood cells in a mild acid - looking for RBC haemolysis indicating increased red blood cell fragility. PNH can then be confirmed using flow cytometry techniques.

The other tests listed here are looking at other hypercoagulable state diagnoses:

- anticardiolipin antibodies for lupus
- antiphospholipid antibodies for APLS
- factor V leiden levels for detection of the factor V leiden mutation
- Coombs' test looking for intravascular haemolysis (which is negative in PNH as the haemolysis in PNH is not caused by antibodies)

Whilst these are all possible diagnoses; they do not fit with the history as well as PNH.

## **Paroxysmal nocturnal haemoglobinuria**

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

### Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

### Features

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

### Diagnosis

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

### Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

### Question 6 of 68

You are looking after a 35-year-old man who is in the oncology day unit receiving his second round of chemotherapy for a low grade non-Hodgkin's lymphoma. His lymphoma is confined to two lymph node groups in his anterior cervical chain and right inguinal region. In total there are 6 nodes with the largest being 4cm in size. He had no issues during his first round of chemotherapy apart from some nausea a week afterwards. He has no other medical problems and is on no other medications. His bloods pre-chemotherapy are as shown below:

Na <sup>+</sup>	137 mmol/l
K <sup>+</sup>	3.8 mmol/l
Urea	2.8 mmol/l
Creatinine	55 µmol/l
Corrected Calcium	2.39 µmol/l
Phosphate	1.05 µmol/l

What regimen would be most appropriate for prevention of tumour lysis syndrome in his case?

[Allopurinol \(200mg BD\)11%](#)[Fluids and allopurinol \(200mg BD\)42%](#)[Fluids and rasburicase \(0.2mg/kg\)26%](#)[Reduced dose chemotherapy3%](#)[Fluids, allopurinol \(200mg BD\) and rasburicase \(0.2mg/kg\)18%](#)

The British Society of Haematology suggest that patients undergoing chemotherapy can be categorised into three different risk groups for tumour lysis syndrome. While you are not required to know how to do this in detail it would be important clinically to be able to recognise factors that put people at increased risk:

- High tumour burden
- High grade tumours with rapid cell turnover
- Pre-existing renal impairment or renal involvement by the tumour
- Increased age
- Treatment with highly active, cell-cycle specific agents
- Concomitant use of drugs that increase uric acid levels (the list is available on the guidance)

<b>Risk Group</b>	<b>Prophylaxis</b>
Low Risk	Adequate hydration (consider IV fluids and allopurinol prophylaxis)
Intermediate Risk	Allopurinol (7 days) and IV fluids
High Risk	Rasburicase and IV fluids (consider low dose chemotherapy)

This patient has no high risk features in his history and is therefore considered low risk, so the closest answer is fluids and allopurinol.

It is important to know that allopurinol and rasburicase should not be used together, as allopurinol reduces the effectiveness of rasburicase. Allopurinol reduces the production of urate, allowing elimination of upstream compounds, which are more water soluble and thus more easy to excrete through the kidneys. Rasburicase, on the other hand, converts urate into more easily excreted downstream compounds.

In addition rasburicase cannot be given to patients with G6PD as it can precipitate haemolysis.

<http://onlinelibrary.wiley.com/doi/10.1111/bjh.13403/epdf>

## **Tumour lysis syndrome**

Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high grade lymphomas and leukaemias. It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. On occasion it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys. Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.

TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a low calcium. It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system -

Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy.

- uric acid > 475umol/l or 25% increase
- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:

- increased serum creatinine (1.5 times upper limit of normal)
- cardiac arrhythmia or sudden death
- seizure

#### Question 1 of 60

A 52-year-old male was seen in the rapid access Transient Ischaemic Attack (TIA) clinic. He presented to his GP with new onset left leg and arm weakness three days ago. The weakness lasted for 90 minutes and fully resolved with no residual defect. He had a past medical history of hypertension, obstructive sleep apnoea and a left sided deep vein thrombosis eight years ago. His medication comprised ramipril 5mg OD. He smoked ten cigarettes per day and did not drink alcohol.

On examination, he had obvious truncal obesity and a flushed complexion. Blood pressure was 128/82 mmHg, heart rate 78/min, respiratory rate 16/min and oxygen saturations 99% on air. Cardiovascular examination revealed a regular pulse and nil else of note. Respiratory and gastrointestinal examination were normal, though examination of the abdomen was somewhat limited by the presence of truncal obesity. Neurological examination was unremarkable with normal cranial nerve, fundoscopy and peripheral neurological examinations.

Initial investigations revealed the following results:

Hb	191 g/l
MCV	98 fl
Hct	0.523
Platelets	502 * 10 <sup>9</sup> /l
WBC	14.0 * 10 <sup>9</sup> /l
Neutrophils	86%
Lymphocytes	10%
Monocytes	4%

HbA1c	43 mmol/mol
Fasting cholesterol	5.6 mmol/l

ECG: 76bpm normal sinus rhythm no other abnormality

Chest x-ray: unremarkable

24 hr ECG: no arrhythmia seen

Echo: normal systolic function, mild aortic stenosis with pressure gradient of 42mmHg

CT head: normal intracranial appearances, no evidence of mass shift, space occupying lesion or haemorrhage

What is the most appropriate next investigation most likely to lead to the underlying diagnosis?

[Cardiac catheterization 6%](#) [Testing for presence of JAK2 mutation 78%](#) [Bone marrow biopsy 6%](#) [Radioisotope scanning of circulating blood volumes 5%](#) [MRI scanning of the abdomen 5%](#)

This gentleman has polycythaemia rubra vera (PRV). Whilst all of the above investigations may facilitate the diagnostic process, this question asks *What is the most appropriate next investigation most likely to lead to the underlying diagnosis?*. Testing for JAK2 mutation has widely surpassed the use of radioisotope scanning and is diagnostic of PRV. It is, therefore, the best option.

### **Polycythaemia vera: features**

Polycythaemia vera (previously called polycythaemia rubra vera) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with polycythaemia vera and this has resulted in significant changes to the diagnostic criteria. The incidence of polycythaemia vera peaks in the sixth decade.

#### **Features**

- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance
- hypertension in a third of patients

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

Other features that may be seen in PRV include a low ESR and a raised leukocyte alkaline phosphatase

The diagnostic criteria for polycythaemia vera have recently been updated by the BCSH. This replaces the previous polycythaemia vera Study Group criteria.

JAK2-positive polycythaemia vera - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count $>450 \times 10^9/l$ )
B2	Neutrophil leucocytosis (neutrophil count $> 10 \times 10^9/l$ in non-smokers; $> 12.5 \times 10^9/l$ in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin



## Question 2 of 60

A 54-year-old alcoholic man with chronic hepatitis C is taken to the emergency department by the police. There it was noted that the man had blisters and crusted lesions on his face and lower arms.

Laboratory tests showed elevated plasma porphyrins and elevated uroporphyrin I in the urine, and isocoproporphyrin in the faeces. Biopsy of the skin lesion showed subepidermal blisters with minimal inflammation, marked solar elastosis, thickening of the vessel wall in the papillary dermis and 'caterpillar bodies' in the roof of the blister.

Which of the following is the most likely diagnosis?

[Acute intermittent porphyria8%Delta-aminolevulinic acid dehydrase deficiency6%Erythropoietic protoporphyria9%Hereditary coproporphyria8%Porphyria cutanea tarda69%](#)

Porphyria cutanea tarda causes chronic blistering and crusting skin lesions on sun-exposed skin. Precipitating factors: iron (even if normal amounts), oestrogen and alcohol use, and chronic hepatitis C infection.

The findings on skin biopsy can help with the diagnosis but are not very specific (the 'caterpillar bodies' are essentially clumps of basement membrane material). The key to the diagnosis is the presentation and porphyrin analysis.

## Porphyrias

### Overview

- abnormality in enzymes responsible for the biosynthesis of haem
- results in overproduction of intermediate compounds (porphyrins)
- may be acute or non-acute



### Acute intermittent porphyria (AIP)

- autosomal dominant

- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms
- hypertension and tachycardia common
- urine turns deep red on standing

#### Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

#### Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

#### Question 3 of 60

A 45-year-old lady presents to the Emergency Department progressive shortness of breath for the last three days. It is worse on activity but is not associated with any cough or wheeze. She has a past medical history of asthma and HIV, for which takes antiretroviral medication regularly. At her last clinic appointment two weeks ago, she was found to have oral candida and so was given a 2 week course of nystatin and started on dapsone for prophylaxis of pneumocystis jirovecii pneumonia. She is a non-smoker.

On examination, her lips and nail beds have a bluish tinge and she is visibly breathless. Her respiratory rate is 26 per minute and on pulse oximetry her saturations are 91% on air both at rest and on exercise. Her temperature is 36.5°C and she has not felt feverish. On auscultation she has vesicular breath sounds with minimal wheeze and normal heart sounds with no murmurs. She has no ankle oedema and JVP is not raised. There is no evidence of oral candidiasis and no lymphadenopathy. Her calves are soft and non-tender.

A chest x-ray shows clear lung fields with no focal consolidation or lymphadenopathy. ECG is sinus rhythm at 90 beats per minute with normal complexes throughout.

Arterial blood gas on air:

pH 7.51  
PaO<sub>2</sub> 13.7 kPa  
PaCO<sub>2</sub> 3.34 kPa  
HCO<sub>3</sub><sup>-</sup> 22.1 mmol/l  
BE -3.3 mmol/l  
sO<sub>2</sub> 97%  
Hb 113 g/l  
Na<sup>+</sup> 143 mmol/l  
K<sup>+</sup> 3.7 mmol/l  
Glu 5.2 mmol/l  
Lac 1.9 mmol/l

What is the most likely diagnosis?

[Acute asthma6%Carbon monoxide poisoning11%Methemoglobinemia61%Pneumocystis jirovecii pneumonia12%Pulmonary embolus10%](#)

This lady has shortness of breath with low saturations on pulse oximetry but normal PaO<sub>2</sub> and saturations on arterial blood gas. This combined with a bluish discolouration and normal chest examination point towards a diagnosis of methemoglobinaemia, a known side effect of the dapsone on which she has been started.

In exacerbation of asthma one would expect wheeze and a low PaO<sub>2</sub>. Carbon monoxide poisoning typically results in cherry red appearance. This lady does not have any history of suggest pulmonary embolus and one would again expect a low PaO<sub>2</sub>, associated with a tachycardia. Pneumocystis pneumonia would be unlikely on prophylaxis, and there may be x-ray changes and drop in saturations on exercise.

Reference: Prchal JT. Clinical features, diagnosis, and treatment of methemoglobinemia. Uptodate. Available online at: <http://www.uptodate.com/contents/clinical-features-diagnosis-and-treatment-of-methemoglobinemia>

## **Methaemoglobinaemia**

Methaemoglobinaemia describes haemoglobin which has been oxidised from  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ . This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as  $\text{Fe}^{3+}$  cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

#### Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

#### Acquired causes

- drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

#### Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal  $\text{pO}_2$  but decreased oxygen saturation

#### Management

- NADH - methaemoglobinaemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

#### Question 8 of 60

A 57-year-old female presents to pre-assessment surgical clinic prior to an elective arthroscopy of her left knee that she injured while playing tennis. She is otherwise asymptomatic, has no other medical history and is a lifelong non-smoker. She drinks 10 units of alcohol per week. Recently, she has experienced hot flushes and irregular periods, which she puts down to undergoing the menopause. Examination of her cardiovascular, respiratory and abdominal systems are unremarkable.

Her blood results are as follows:

Hb	95 g/l
MCV	59 fl
Platelets	$389 \times 10^9/l$
WBC	$4.5 \times 10^9/l$
Red cell distribution width	13% (normal range 11.5-14.5%)
Blood film	anisocytosis, hypochromia, target cells

Which investigation is most likely to reveal the diagnosis?

[Serum ferritin 23%](#) [Total iron binding capacity 16%](#) [Serum iron 11%](#) [Haemoglobin electrophoresis 39%](#) [Bone marrow biopsy 10%](#)

The patient is asymptomatic with a microcytic anaemia. Note the disproportionately lower MCV compared to the level of haemoglobin and the normal red cell distribution width: the first is a distinctive feature of thalassaemia beta minor (trait) while the second suggests that all red cells made by the marrow of similar haemoglobin quality, such as in an underlying genetic trait such as thalassaemia beta minor. In contrast, iron deficiency normally demonstrates a significant haemoglobin drop by the time MCV is at such a low value while increasing the RDW during early to mid stages of iron deficiency, as some red cells are produced normally while some are profoundly microcytic.

Diagnosis of thalassaemia beta minor is by haemoglobin electrophoresis. However, diagnosis of iron deficiency is reliant on a combination of indicators: serum iron alone is not necessarily diagnostic as it also appears in anaemia of chronic disease. Serum ferritin is perhaps the most reliable indicator of plasma and marrow iron stores but be wary that it may be increased in inflammatory states, hence mask an underlying iron deficiency anaemia. Total iron binding capacity (TIBC) is a measure of transferrin, to which iron is bound to in plasma. Again, it is a useful indicator of iron stores but can be altered by pregnancy or the oral contraceptive pill. An iron deficiency anaemia picture is generally diagnosed by a combination of all three: low serum iron, high TIBC, low ferritin.

### **Beta-thalassaemia trait**

The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. Beta-thalassaemia trait is an autosomal recessive condition characterised by a mild hypochromic, microcytic anaemia. It is usually asymptomatic

Features

- mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia
- HbA2 raised ( $> 3.5\%$ )

#### Question 1 of 49

A 57-year-old presents with recurrent episodes of bleeding gums, nosebleeds and intermittent haematuria over the past 6 weeks. He works as an accountant, does not have any past medical history but is an active smoker of 20 pack years. He drinks occasional alcohol.

On examination, scabs and dried blood are noted on mucous membranes. No arthritis or cutaneous abnormalities are noted. The nasal bridge is unremarkable. His conjunctiva appeared pale, respiratory, abdominal and cardiovascular examination was unremarkable. His blood tests are as follows:

Hb            37 g/l  
 MCV        87 fl  
 Platelets     $17 \times 10^9/l$   
 WBC         $44.0 \times 10^9/l$

Blood film myeloblasts with elongated, needle-like cytoplasmic inclusions

Na<sup>+</sup>        147 mmol/l  
 K<sup>+</sup>        3.2 mmol/l  
 Urea        7.8 mmol/l  
 Creatinine 70  $\mu$ mol/l

What is the most likely underlying diagnosis?

[Acute myeloid leukaemia66%](#) [Acute lymphocytic leukaemia7%](#) [Chronic myeloid leukaemia12%](#) [Chronic lymphoid leukaemia5%](#) [Myelofibrosis11%](#)

The diagnosis is made on blood film description of needle-like elongated cytoplasmic inclusions, known as Auer rods that are pathognomonic of acute myeloid leukaemia, with myeloblasts typical of myeloid leukaemias. Clinical features are frequently typical of cell line abnormalities secondary to marrow infiltration (shortness of breath on exertion, pallor caused by anaemia; bruising or bleeding caused by thrombocytopaenia) and infections secondary to dysfunctional white cells. Diagnosis is confirmed by bone marrow biopsy, with blast cells accounting for greater than 20% of marrow cellularity. Immunophenotyping, cytogenetic and morphological analysis guides subsequent treatment options.

## Acute myeloid leukaemia

Acute myeloid leukaemia is the more common form of acute leukaemia in adults. It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.

Poor prognostic features

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7

Acute promyelocytic leukaemia M3

- associated with t(15;17)
- fusion of PML and RAR-alpha genes
- presents younger than other types of AML (average = 25 years old)
- Auer rods (seen with myeloperoxidase stain)
- DIC or thrombocytopenia often at presentation
- good prognosis

Classification - French-American-British (FAB)

- M0 - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- M3 - acute promyelocytic
- M4 - granulocytic and monocytic maturation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 - megakaryoblastic

Question 2 of 49

A 50-year-old man is diagnosed with high-grade non-Hodgkin's lymphoma and starts his regimen of R-CHOP chemotherapy. Two days after his chemotherapy he complains of feeling increasingly weak, lethargic and generally unwell. He has developed persistent vomiting and is

unable to tolerate oral fluids.

He has a history of recurrent gout but has been unable to tolerate allopurinol.

On examination, he looks unwell and pale. He seemed short of breath with a respiratory rate of 28 per minute. His temperature is 36.5°C, heart rate 110 bpm, blood pressure 100/60 mmHg.

His heart sounds were normal. His JVP was raised by 4cm lying at 45 degrees in the bed. Examination of the chest revealed fine bibasal inspiratory crepitations. Pitting oedema was present to mid-shins bilaterally.

Abdominal examination was unremarkable.

On neurological examination, there was normal tone and sensation to all limbs. General weakness was noted.

The house officer has taken bloods:

Na+	137 mmol/L
K+	6.2 mmol/L
Urea	15 mmol/L (previously 8)
Creatinine	240 µmol/L (previously 100)
Hb	100 g/L
WBC	10.0x10 <sup>9</sup> /L
Corrected Calcium	1.95 mmol/L
Phosphate	2.3 mmol/L
Uric acid	640 mmol/L
LFTs	Normal

Chest x-ray shows congested lung fields.

ECG demonstrates tall T waves.

In view of the diagnosis which of the following is most likely to treat the hyperuricaemia?

[IV calcium gluconate, insulin and dextrose infusion10% Allopurinol6% Rasburicase68% IV fluids13% IV electrolyte replacement3%](#)

This man has lymphoma and has presented with physical and biochemical markers suggesting established tumour lysis syndrome. He has severe electrolyte disturbance: hyperkalaemia, hypocalcaemia, hyperphosphataemia. The chest x-ray suggests pulmonary oedema and ECG indicates a degree of cardiac toxicity from the hyperkalaemia. There is also acute renal failure and hyperuricaemia.



The question asks what treatment should be used to treat the underlying condition of tumour lysis syndrome. The answer is rasburicase as he has previously been intolerant of allopurinol in the context of gout prophylaxis. All the other answers are entirely reasonable and are part of the treatment of tumour lysis syndrome but do not answer this question specifically.

## **Tumour lysis syndrome**

Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high grade lymphomas and leukaemias. It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. On occasion it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys. Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.

TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a low calcium. It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system -  
Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy.

- uric acid > 475umol/l or 25% increase
- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:

- increased serum creatinine (1.5 times upper limit of normal)
- cardiac arrhythmia or sudden death
- seizure

### Question 5 of 49

A 72-year-old woman presents to the emergency department with a painful and swollen leg. This has developed over two days, and she otherwise feels well in herself. She was recently away on holiday to Spain and returned four weeks ago. She is able to mobilise independently and has had no reduced periods of mobility. She has a background breast cancer diagnosed four years ago, which unfortunately relapsed and spread into her liver. She is now on hormonal treatment only.

On examination, her left leg is swollen and red, and the calf diameter is significantly larger on the left side. A doppler ultrasound scan demonstrates a left-sided deep vein thrombus. What is the most appropriate anticoagulation strategy?

[Three months of low molecular weight heparin11%](#)[Six months of low molecular weight heparin69%](#)[Six months of a new oral anticoagulant \(NOAC\)5%](#)[Three months of warfarin8%](#)[Six months of warfarin7%](#)

The correct answer is six months of low molecular weight heparin (LMWH). LMWH heparin is preferred to warfarin and NOACs in malignancy due to differences in efficacy. As active cancer is likely to cause a continued pro-coagulopathic state, it is recommended to continue LMWH for at least six months.

Source:

'Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing Clinical Guideline [CG144]'. National Institute of Clinical Excellence. N.p., 27 June 2012.

## Deep vein thrombosis: diagnosis and management

### Diagnosis

NICE published guidelines in 2012 relating to the investigation and management of deep vein thrombosis (DVT).

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

### Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring	1

<b>Clinical feature</b>	<b>Points</b>
general or regional anaesthesia	
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

#### Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
- a proximal leg vein ultrasound scan within 4 hours
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

#### Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range

- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months

### **Further investigations and thrombophilia screening**

As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:

- a physical examination (guided by the patient's full history) and
- a chest X-ray and
- blood tests (full blood count, serum calcium and liver function tests) and urinalysis.

Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

### **Thrombophilia screening**

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

### **Question 6 of 49**

A 45-year-old worker on demolition sites comes to the Emergency department for review. He has suffered increasing tiredness, lethargy, headache, and abdominal pains over the past 2 months. On examination he is hypertensive with a blood pressure of 155/90 mmHg, his pulse is 85 beats per minute and regular. He looks pale.

## Investigations

Hb 97 g/l  
MCV 78 fl  
Platelets  $175 \times 10^9/l$   
WBC  $6.2 \times 10^9/l$   
Lead 5  $\mu\text{mol/l}$

Blood film reveals basophilic stippling

Which of the following is the most appropriate initial intervention?

[Activated charcoal4% Disodium EDTA38% DMSA43% Haemodialysis8% Vitamin C7%](#)

DMSA is an oral chelation therapy that can be used for chronic lead poisoning, the diagnosis here. A lead level above  $3.4 \mu\text{mol/l}$  indicates significant occupational exposure and that the patient should be withdrawn from work. 500mg twice per day is a usual initial therapeutic dose.

Given his lead exposure represents chronic exposure, there is no role for activated charcoal. Disodium EDTA is used in the management of acute lead poisoning and is given intravenously. Human trials of vitamin C with respect to treatment of lead toxicity are so far equivocal, and there is no role for haemodialysis in chronic lead poisoning.

## Lead poisoning

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs

### Features

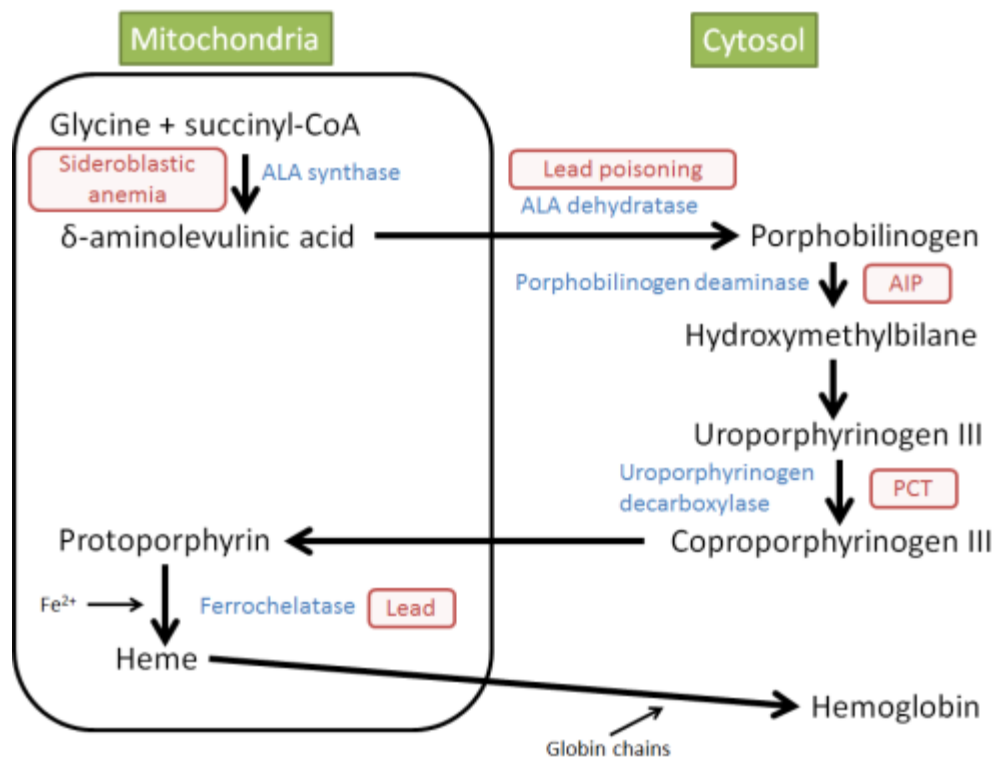
- abdominal pain
- peripheral neuropathy (mainly motor)
- fatigue
- constipation
- blue lines on gum margin (only 20% of adult patients, very rare in children)

## Investigations

- the blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- full blood count: microcytic anaemia. Blood film shows red cell abnormalities including basophilic stippling and clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA
- dimercaprol



A 23-year-old medical student went to Uganda on his elective but has had to return to the UK early due to illness. He had been careful to take malaria prophylaxis and slept under a mosquito net. He was using primaquine due to previous intolerable side effects with doxycycline. He was complaining of central abdominal pain and had noticed jaundiced sclera in the few days prior to returning to the UK. There is no relevant past medical history and he takes no regular medication. He is a non-smoker and drinks 2-4 units of alcohol weekly.

Observations show a blood pressure of 110/73 mmHg and heart rate of 98 beats per minute. He is afebrile, has a respiratory rate of 16 per minute and oxygen saturations of 94% on room air.

On examination, he is pale and jaundiced with yellow sclera. There is no cyanosis. His chest sounds clear and heart sounds are normal with nil added. The abdomen is soft, generally tender but with no guarding or peritonism. Bowel sounds are normal.

Bloods show the following:

Haemoglobin	86 g/L	Sodium	139 mmol/L
Platelets	188 x10 <sup>9</sup> /L	Potassium	3.6 mmol/L
White cell count	11.0 x10 <sup>9</sup> /L	Urea	3.0 mmol/L
Neutrophils	8.5 x10 <sup>9</sup> /L	Creatinine	62 micromol/L
Reticulocytes	11%	Albumin	34 g/L
CRP	7 mg/L	Bilirubin	67 micromol/L
ALT	21 iu/L		
Alkaline Phosphatase	40 iu/L		

Peripheral blood film:

- Heinz bodies seen with methyl violet staining.
- Bite and blister cells also present.

What is the most likely diagnosis?

[G6PD deficiency 78%](#)[\*Plasmodium falciparum\* infection 6%](#)[\*Mycoplasma pneumoniae\* 4%](#)[Hereditary spherocytosis 7%](#)[Lead poisoning 5%](#)

This student has acute haemolytic anaemia (anaemia, reticulocytosis and raised bilirubin with normal ALT). Answers A, C, D and E are all causes of haemolytic anaemia.

The blood film is the main diagnostic tool to differentiate between these answers. Heinz bodies, bite and blister cells are all seen in acute haemolysis associated with G6PD deficiency. The acute haemolysis has been triggered by antimalarial treatment (usually primaquine).

A blood film of hereditary spherocytosis shows spherocytes and reticulocytes. In lead poisoning, there should be dimorphic cells with ring granules on Perl's staining.

*Plasmodium falciparum* is a common form of malaria that multiplies in the liver. Infection with this can cause anaemia with abnormal liver function tests (LFTs). Persons with G6PD deficiency are somewhat protected from infection with *Plasmodium falciparum* and *Plasmodium vivax* malaria.

G6PD deficiency is X-linked and is more prevalent in Mediterranean populations.

## **G6PD deficiency**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest red blood cell enzyme defect. It is more common in people from the Mediterranean and Africa and is inherited in a X-linked recessive fashion. Many drugs can precipitate a crisis as well as infections and broad (fava) beans

### Pathophysiology

- $\downarrow$  G6PD  $\rightarrow$   $\downarrow$  glutathione  $\rightarrow$  increased red cell susceptibility to oxidative stress

### Features

- neonatal jaundice is often seen
- intravascular haemolysis
- gallstones are common
- splenomegaly may be present
- Heinz bodies on blood films

Diagnosis is made by using a G6PD enzyme assay

Some drugs causing haemolysis

- anti-malarials: primaquine
- ciprofloxacin
- sulph- group drugs: sulphonamides, sulphasalazine, sulfonylureas

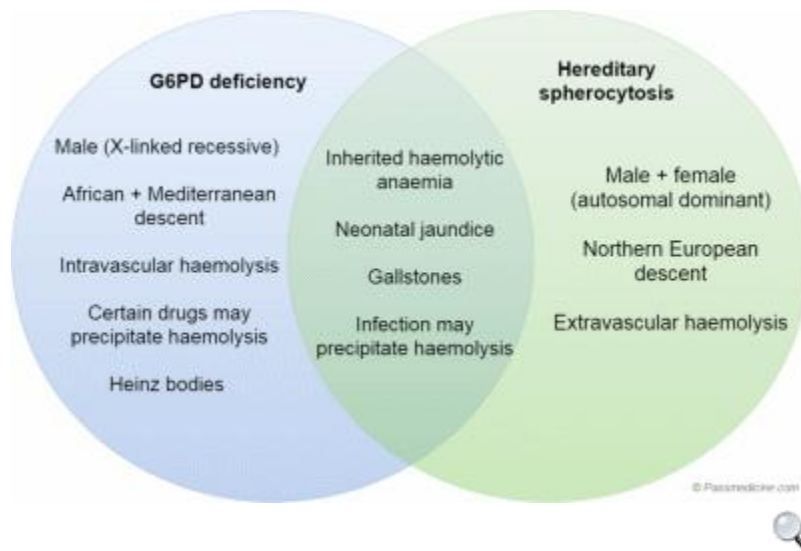
Some drugs thought to be safe

- penicillins



- cephalosporins
- macrolides
- tetracyclines
- trimethoprim

Comparing G6PD deficiency to hereditary spherocytosis:



Comparison of G6PD deficiency to hereditary spherocytosis

	G6PD deficiency	Hereditary spherocytosis
<b>Gender</b>	Male (X-linked recessive)	Male + female (autosomal dominant)
<b>Ethnicity</b>	African + Mediterranean descent	Northern European descent
<b>Typical history</b>	<ul style="list-style-type: none"> <li>• Neonatal jaundice</li> <li>• Infection/drugs precipitate haemolysis</li> <li>• Gallstones</li> </ul>	<ul style="list-style-type: none"> <li>• Neonatal jaundice</li> <li>• Chronic symptoms although haemolytic crises may be precipitated by infection</li> <li>• Gallstones</li> <li>• Splenomegaly is common</li> </ul>
<b>Blood film</b>	Heinz bodies	Spherocytes (round, lack of central pallor)
<b>Diagnostic test</b>	Measure enzyme activity of G6PD	Osmotic fragility test

### Question 1 of 39

A 62-year-old gentleman with a background of Rheumatoid Arthritis, on maintenance sulfasalazine, is referred to the medical team from his GP with severe unremitting flu-like symptoms and deranged blood tests.

On examination, his temperature is 38.3 degrees celsius, heart rate 104bpm, respiratory rate 31/min and oxygen saturations 92% on room air.

His blood test reveals the following:

Hb	82 g/l
Platelets	$52 \times 10^9/l$
WBC	$18 \times 10^9/l$
Ferritin	50,000ng/ml
EBV Monospot test	+ve

He is initially treated as neutropaenic sepsis, with broad spectrum antimicrobials, and transferred to the intensive care unit for organ support. Unfortunately, he does not make any improvement. He is then seen by haematology who organise a bone marrow aspirate, revealing haemophagocytosis. What is the most likely underlying diagnosis?

[Macrophage activation syndrome50%](#)[Drug-induced pancytopenia8%](#)[Atypical infection5%](#)[Parvovirus infection15%](#)[Felty syndrome23%](#)

Macrophage activation syndrome is a condition characterised by excessive immune stimulation and cytokine storm in a rheumatological patient with an intercurrent EBV infection.

There is no suggestion in the question that there is a parvovirus infection and Felty syndrome would be characterised by a neutropaenia and splenomegaly. Drug-induced pancytopenia and atypical infections would not commonly show haemophagocytosis in the bone marrow.

### Macrophage activation syndrome

Macrophage activation syndrome is a rare disorder that is associated with rheumatological conditions such as juvenile idiopathic arthritis, rheumatoid arthritis or systemic lupus erythematosus. It commonly presents with a pancytopenia and intercurrent infection - particularly EBV - and is usually initially treated as neutropaenic sepsis.

Left untreated, the disease is often fatal after two months.

- Diagnosis: bone marrow aspiration can reveal haemophagocytosis as the key feature.
- Other features: excessive hyperferritinemia, elevated triglycerides, deranged LFTs, and hypofibrinogenemia.
- Treatment: immunosuppression.

#### Question 2 of 39

A 70-year-old man is referred to the haematology clinic by his general practitioner with anaemia. He has experienced progressive fatigue and shortness of breath for four months. On further questioning he also describes waking up at night soaked in sweat on one or two nights per week for the last month. His weight is stable. He has a past medical history of hypertension and COPD.

On examination he is pale. His heart sounds are normal and his chest is clear.. He has no ankle oedema and JVP is not raised. His abdomen is soft and he has splenomegaly 3cm below the costal margin with no hepatomegaly.

Test results sent with him by his GP are as follows:

Hb	92 g/l	Na <sup>+</sup>	143 mmol/l
Platelets	143 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.7 mmol/l
WBC	4 * 10 <sup>9</sup> /l	Urea	7 mmol/l
Neuts	2 * 10 <sup>9</sup> /l	Creatinine	86 µmol/l
Lymphs	1 * 10 <sup>9</sup> /l	CRP	5 mg/l

Blood film: Anisocytosis with mild hypochromia. Tear drop cells. Mild thrombocytopenia with no platelet clumping.

Chest x-ray: Mildly hyperexpanded lung fields. No focal consolidation. No masses or lymphadenopathy.

Upper GI endoscopy & colonoscopy: Normal

Presence of which mutation is required to confirm the likely diagnosis?

[BCR-ABL25%BCL210%C-MYC19%JAK238%TP538%](#)

This gentleman has B symptoms, anaemia and splenomegaly in the presence of characteristic tear drops cells on the blood film, making myelofibrosis the most likely diagnosis. The British Committee for Standards in Haematology list several mutations which together with these symptoms and fibrosis on bone marrow form the diagnostic criteria. The most common of these is JAK2.

Presence of BCR-ABL is diagnostic for CML. BCL2 and TP53 mutations are seen in diffuse large B cell lymphoma.

C-MYC mutations are seen in Burkitt's lymphoma.

Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis 2012. British Journal of Haematology, 2014;:167;418438.

## **Myelofibrosis**

### Overview

- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen

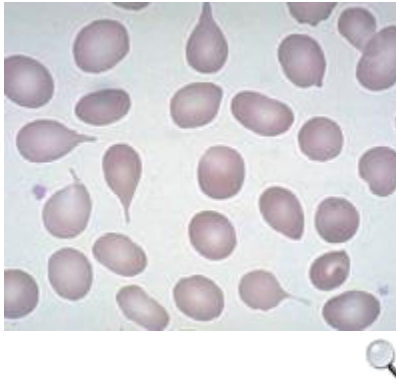
### Features

- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- massive splenomegaly
- hypermetabolic symptoms: weight loss, night sweats etc

### Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film

- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

#### Question 4 of 39

A 37-year-old woman was admitted to the Intensive Care Unit (ICU) two days following chemotherapy. She had received her third of six cycles of chemotherapy for malignant ovarian cancer and without initial complication and was discharged the same day. Two days later she felt unwell and developed a fever. After liaising with the oncology unit she was admitted directly to the Medical Admission Unit. A full septic screen was conducted and she was treated empirically for neutropaenic sepsis with intravenous tazocin and gentamicin. Other than malignant ovarian cancer her past medical history was unremarkable, and there was no known metastasis. She was not taking any other drug therapy and was a non smoker. She did not consume alcohol.

Unfortunately whilst on the Medical Admission Unit she continued to deteriorate, developing fluctuating hemiparesis of initially the left lower limb, and then the right upper limb. Her level of consciousness dropped and her speech had become slurred. An urgent transoesophageal echocardiogram and CT head scan was conducted, pending availability of a MRI scan. She was promptly transferred to the Intensive Care Unit.

Upon arrival at the ICU she appeared very unwell, with a GCS of 12/15. Her blood pressure was 188/96 mmHg, her heart rate was 112, her respiratory rate was 22/min and her temperature was 38.5 degrees celsius. Examination of the cardiovascular system revealed the presence of normal heart sounds, a JVP of 3cm and warm well perfused peripheries. Examination of the respiratory system revealed good air entry in both lungs, with an oxygen saturation of 95% on air. Examination of her gastrointestinal system was unremarkable. Examination of her neurological system revealed localization to pain stimulus, with confusion and eye opening only in response to verbal prompting. Her speech was slurred. There was no other apparent focal neurological deficit, with otherwise normal cranial nerve and peripheral nervous system testing.

The results of the investigations conducted are as follows:

Hb	89g/l
Platelets	$38 \times 10^9/l$
WBC	$15.2 \times 10^9/l$
Reticulocyte count	4% (ie above normal range)
Blood film	presence of schistocytes, normocytic normochromic anaemia

Na <sup>+</sup>	136 mmol/l
K <sup>+</sup>	6.1 mmol/l
Urea	10.1 mmol/l
Creatinine	154 $\mu$ mol/l

CRP	22 mg/l
ESR	45 mm/hr
Protein	78 g/l
Albumin	36 g/l
Adj calcium	2.42 mmol/l
Phosphate	0.95 mmol/l
Bilirubin	44 $\mu$ mol/l
ALT	39 u/l
LDH	1286 u/l
ALP	102 u/l
PTT	14s
APTT	44s
INR	1.1
D-dimer	136 ng/ml

Chest x-ray: normal heart and lung appearances

ECG: heart rate 107bpm normal sinus rhythm, normal QRS and QTc intervals

Urinalysis: proteinuria ++, haematuria +, leuc/nit/glu negative

Blood MCS x3: pending result

Urine MCS: pending result

CT head: no space occupying lesion, mass shift or intracerebral haemorrhage seen

Transoesophageal echocardiogram: normal systolic function, normal appearance of all valves, no evidence of vegetation seen

In the context of the likely underlying diagnosis, what is the best immediate management step?

[Commence immediate plasma exchange 74%](#)[Commence high dose intravenous hydrocortisone 8%](#)[Commence platelet infusion 4%](#)[Commence IV meropenem and IV antifungal therapy 8%](#)[Commence fresh frozen plasma infusion 6%](#)

This patient has developed thrombotic thrombocytopenia purpura (TTP) secondary to chemotherapy, as manifested by the combination haemolytic anaemia, thrombocytopenia and acute renal impairment. The presence of a fever and neurological involvement differentiates this condition from haemolytic-uraemic syndrome. Of the above options, plasma exchange holds the best prognosis for this condition and is, therefore, the best option to be initiated without delay, but in practice glucocorticoids and fresh frozen plasma infusions are often given pending arranging plasma exchange.

### **Thrombotic thrombocytopenic purpura: management**

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

Question 5 of 39

A 30-year-old woman presents to the emergency department with severe, progressive abdominal pain over the past day. The pain is accompanied by nausea, vomiting and diarrhoea. The patient recalls similar episodes in the past that progressed over a few days and lasted for a week. Temperature is 37°C, blood pressure is 140/100 mmHg, pulse is 120/min and respirations are 16/min.

On examination: minimal abdominal tenderness and rebound tenderness. She has a history of abdominal surgery for suspected appendicitis and biliary disease, neither of which was confirmed once inside the abdomen.

Which of the following will help to confirm the diagnosis?

[Erythrocyte porphyrins4% Faecal porphyrins5% Plasma porphyrins6% Urine porphobilinogen64% Urine porphyrins21%](#)

This patient has acute intermittent porphyria, which classically presents with neurovisceral symptoms which can mimic an acute abdomen. This mimicry occurs because the abdominal pain is produced by a nerve problem rather than inflammation, hence why exploratory surgery is uneventful. In long-standing cases, patients may have damage to their motor nerves resulting in upper limb weakness.

### **Acute intermittent porphyria**

Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

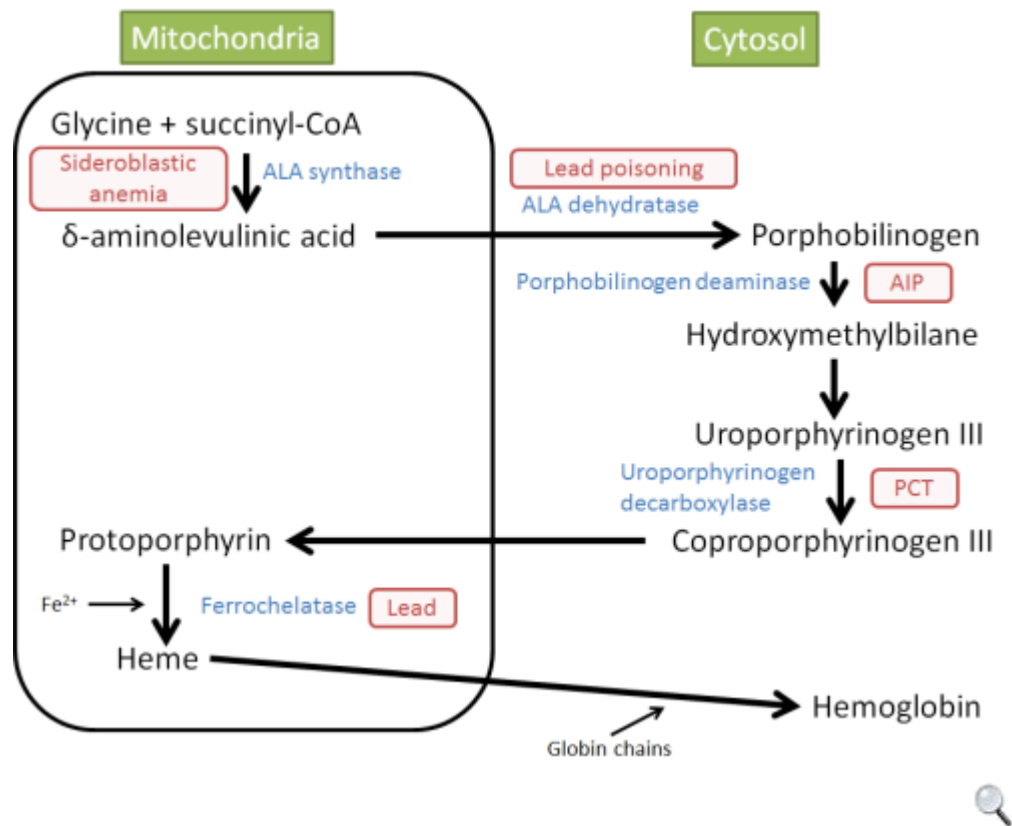
#### **Features**

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

#### **Diagnosis**

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen





#### Question 6 of 39

A 60-year-old man is seen in the ambulatory care clinic with a two week history of reduced urine output. This has been associated with a general malaise and fatigue. He denies any fever, abdominal pain, dysuria or change in flow. He has a past history of multiple myeloma, hypertension and benign prostatic hypertrophy. He has been on lenalidomide and dexamethasone chemotherapy for the last four months and was told at a clinic appointment one month ago that there were no problems with his blood results. His other medications are ramipril, finasteride and tamsulosin, and these have not been altered in many years.

On examination he appears fatigued and pale. His abdomen is soft with no palpable masses.

His investigation results are as follows:

Urine dip:

Blood -

Protein      ++  
Ketones      -  
Leucocytes +  
Nitrites      -

Blood tests:

Hb          110 g/l  
Platelets 130 \* 10<sup>9</sup>/l  
WBC      9 \* 10<sup>9</sup>/l

Na<sup>+</sup>          139 mmol/l  
K<sup>+</sup>          4.7 mmol/l  
Urea          10 mmol/l  
Creatinine 184 µmol/l  
Ca<sup>2+</sup>        2.3 mmol/l

Which investigation is most likely to reveal the cause of his renal failure?

[Blood film7%](#)[Mid-stream urine4%](#)[Serum free light chains43%](#)[Serum protein electrophoresis23%](#)[Ultrasound renal tract23%](#)

In the absence of any symptoms of obstruction or infection, this gentleman's renal failure likely results from progression of his multiple myeloma. Importantly, calcium is normal. Although blood film, serum protein electrophoresis and serum free light chains are all likely to be abnormal, it is the serum free light chains that are the direct cause of damage to the nephrons in myeloma and are likely to have increased since this gentleman's last follow-up.

In practice, ultrasound renal tract and mid-stream urine would still be performed to exclude obstruction and infection respectively.

Reference: Bird JM et al. Guidelines for the diagnosis and management of multiple myeloma 2014. British Committee for Standards in Haematology. 2014.

## **Myeloma**

### Overview

- neoplastic proliferation of bone marrow plasma cells

- peak age = 70 years
- equal sex ratio

#### Monoclonal products produced

- IgG (50-60%)
- IgA (20-30%)
- light chain disease (20%)

#### Question 8 of 39

A 57-year-old man presents to his General Practitioner with persistent headaches and blurred vision. The symptoms have been present over the past six months but have worsened in recent weeks. On close questioning, the patient also reported a feeling of general fatigue and intermittent muscle aches.

One year previously, the patient had been diagnosed with obstructive sleep apnoea secondary to morbid obesity and had been provided with non-invasive ventilation to use at night. However, the patient admitted that he rarely used this equipment due to a dislike for the tight face mask. Despite dietary and lifestyle advice the patient had gained 6 kg over the past year and had a BMI of 41 kg / m<sup>2</sup>.

Neurological examination including fundoscopy was unremarkable. There were no tender or inflamed joints. Blood tests requested by the GP are detailed below.

Haemoglobin	195 g/L
White cell count	$7.5 \times 10^9/l$
Neutrophils	$5.7 \times 10^9/l$
Lymphocytes	$0.9 \times 10^9/l$
Platelets	$195 \times 10^9/l$
Packed cell volume	0.60
Urea	5.9 mmol / L
Creatinine	110 $\mu$ mol / L
Sodium	135 mmol / L
Potassium	4.1 mmol / L
eGFR	68 ml / min

Review of a full blood count performed 4 months previously was remarkable for previously unnoticed elevated PCV of 0.56. The patient was urgently referred to haematology for further management.

What is the most appropriate treatment for this patient's erythrocytosis?

[Aspirin6% Venesection 43% Hydroxyurea10% Improved compliance with nocturnal non-invasive ventilation34% Referral to weight management service 6%](#)

This patient has a secondary erythrocytosis secondary to hypoxia associated with his obstructive sleep apnoea. He is presenting with significant symptoms of hyperviscosity and should be considered to be at significant risk of thrombotic complications.

Evidence from small case series suggests that erythrocytosis secondary to OSA should be treated with venesection in the presence of hyperviscosity symptoms or a PCV > 0.56. A target PCV of 0.50-0.52 has been shown to increase exercise tolerance.

Aspirin is the mainstay of treatment in polycythaemia vera and cytoreductive treatments such as hydroxyurea are used in high-risk cases.

While weight-loss and improved compliance with OSA treatment may improve erythrocytosis these interventions are likely to require significant time prior to yielding any symptomatic benefit.

Keohane C, McMullin M, Harrison C. The diagnosis and management of erythrocytosis. BMJ 2013;347:f6667.

## **Polycythaemia**

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Relative causes

- dehydration
- stress: Gaisbock syndrome

Primary

- polycythaemia rubra vera

## Secondary causes

- COPD
- altitude
- obstructive sleep apnoea
- excessive erythropoietin: cerebellar haemangioma, hypernephroma, hepatoma, uterine fibroids\*

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia red cell mass studies are sometimes used. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

\*uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem

## Question 9 of 39

A 68-year-old female, presents with lethargy and anorexia. She underwent a partial gastrectomy 3 years ago for bleeding gastric ulcer. Her blood results showed:

Hb	90 g/l
MCV	109 fL
Platelets	$60 \times 10^9/l$
WBC	$3.5 \times 10^9/l$
Blood film	Oval erythrocytes, macrocytic erythrocytes, hypersegmented neutrophils, low platelets and basophilic stippling

What is the underlying diagnosis?

[Sideroblast anaemia 17% Spur cell haemolysis 4% Vitamin-B12 deficiency 64% Thalassaemia 4% Myelodysplasia 11%](#)

Gastrectomy is defined as partial when a part of the stomach is removed surgically and as total when the entire stomach is removed. Typical indications are gastric cancer, recurrent gastric ulcers, large duodenal perforations, bleeding gastric ulcers and gastrointestinal stromal tumours. Malnutrition is less common after partial than after total gastrectomy, but the key nutritional deficiencies are iron-deficiency anaemia, calcium deficiency, and vitamin B12 deficiency. However, the hypersegmented neutrophils are strongly suggestive of B12 deficiency.

Hypersegmented neutrophils are hallmarks of B12 deficiency in multiple choice questions.

## Macrocytic anaemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

### Megaloblastic causes

- vitamin B12 deficiency
- folate deficiency

### Normoblastic causes

- alcohol
- liver disease
- hypothyroidism
- pregnancy
- reticulocytosis
- myelodysplasia
- drugs: cytotoxics

### Question 1 of 29

A 19-year-old man is referred to see you as he has been suffering from recurrent epistaxis and he tells you that if he accidentally injures himself the wound bleeds for a long time.

Initial blood tests are as follows:

Hb	101 g/l
MCV	79 fl
Platelets	$298 \times 10^9/l$
WBC	$9.2 \times 10^9/l$
Bleeding time	Prolonged
PT	14 seconds
APTT	28 seconds
LDH	290 u/l (240 - 480 u/L)
Factor VIIIc	low
Ristocetin platelet aggregation test	Impaired aggregation

What is the single most likely diagnosis?

[Haemophilia A22%](#)[Haemophilia B9%](#)[Haemophilia C4%](#)[Idiopathic Thrombocytopenic Purpura \(ITP\)4%](#)[von Willebrand's disease60%](#)

This patient has a coagulopathy and normal platelets, which immediately excludes ITP. Factor VIIIc is low, meaning that the diagnosis must either be haemophilia A or von Willebrand's disease. In this patient two things favour the diagnosis of von Willebrand's over haemophilia A. Firstly, the bleeding time is prolonged and secondly, the platelet aggregation is impaired in response to ristocetin. Both of these would be normal in haemophilia.

## **Von Willebrand's disease**

Von Willebrand's disease is the most common inherited bleeding disorder. The majority of cases are inherited in an autosomal dominant fashion\* and characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemarthroses and muscle haematomas are rare

### Role of von Willebrand factor

- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

### Types

- type 1: partial reduction in vWF (80% of patients)
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive)

### Investigation

- prolonged bleeding time
- APTT may be prolonged
- factor VIII levels may be moderately reduced
- defective platelet aggregation with ristocetin

### Management

- tranexamic acid for mild bleeding
- desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells

- factor VIII concentrate

\*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

#### Question 2 of 29

A 32-year-old male presents with a progressive worsening non-specific lethargy. 9 months ago, he had returned from an active holiday from New Zealand and now feels lethargic to the point that he can no longer work in his job as a computer programmer. In this period, he has been treated for two deep vein thromboses with low molecular heparin, the first initially attributed to his return flight from New Zealand. He reports three episodes of rose coloured urine over the past 4 months and intermittent episodes of abdominal cramps that his GP had diagnosed to be irritable bowel syndrome.

On examination, you note mild conjunctival pallor and jaundiced sclera. Respiratory, cardiovascular and abdominal examinations are unremarkable. His blood results are as follows:

Hb	76 g/l
MCV	92 fl
Platelets	$276 \times 10^9/l$
WBC	$4.1 \times 10^9/l$
Reticulocytes	18%
Haptoglobin	2 (normal range 41-165 mg/dL)
LDH	2128 (normal range 140-280 units/L)
Coombs' test	negative at 4 and 37 degrees

What is the definitive treatment for the underlying condition?

[Packed red blood cell transfusion14%](#) [Anti-retroviral treatment10%](#) [Bone marrow transplant50%](#) [R-CHOP chemotherapy21%](#) [Intravenous iron replacement5%](#)

This is a tricky clinical scenario with a number of red herrings: a young man in his 30s has presented with recurrent DVTs, episodes of haematuria, abdominal cramps and a blood picture suggestive of intravascular haemolysis (low haptoglobin, raised LDH) not secondary to an autoimmune cause (Coombs negative): there is thus an underlying red cell fragility predisposing to thrombosis, strongly suggestive of paroxysmal nocturnal haemoglobinuria (PNH). Note that haemoglobinuria is not restricted to night-time alone. The majority of patients present in their 30s with thromboses being the most common cause of death.

PNH is caused by an underlying reduced CD 59 on the red cell surface, leading to increased



susceptibility to complement lysis. Complications can present following the release of haemoglobin, such as pulmonary hypertension, dystonia and renal impairment while PNH can overlap with aplastic anaemia and myelodysplasia. PNH patients are managed by blocking complement lysis with eculizumab and red cell transfusions but the only curative solution is allogenic bone marrow transplantation.

## **Paroxysmal nocturnal haemoglobinuria**

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

### Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

### Features

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

### Diagnosis

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

### Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

#### Question 4 of 29

A 44-year-old male presents with a 2-month history of increasing lethargy. His wife reports him to be not quite himself for the past 2 months now, with poor oral intake and poor appetite. He is a self-employed software engineer but currently is unable to work due to his lethargy. He was previously treated for Hodgkin's lymphoma 5 years ago and has since been in remission.

On examination, he has no conjunctival pallor, is dry on his mucous membranes and extremely lethargic. Firm, rubbery lymph nodes are noted in the right axilla. Cardiovascular examination reveals a soft systolic murmur, respiratory and abdominal examinations are unremarkable. He is a non-smoker and drinks alcohol only occasionally. His blood tests are as follows:

Hb	88 g/l
MCV	104 fl
Platelets	$94 \times 10^9/l$
WBC	$12.8 \times 10^9/l$
Red cell distribution	9% (normal 11.5-14.5%)
Blood film	leucoerythroblastic with myeloblasts

What is the most likely cause of this patient's anaemia?

[B12 and folate deficiency](#)11% [Iron deficiency](#)3% [Anaemia of chronic disease](#)4% [Myelodysplasia post-chemotherapy](#)35% [Marrow infiltration](#)47%

This patient has a symptomatic macrocytic anaemia, of which B12 and folate deficiency, myelodysplasia post-chemotherapy and marrow infiltration could all be causes. Iron deficiency results in a microcytic anaemia while anaemia of chronic disease typically causes a microcytic or normocytic anaemia. Blood cells in B12 and folate deficiency are typically megaloblastic, large immature red cells caused by impaired DNA synthesis. Myelodysplasia typically results in red cells of abnormal shapes (poikilocytosis) and sizes (anisocytosis) with Pappenheimer bodies (abnormal granules of iron). Chemotherapy is a possible cause of myelodysplasia but typically after recent treatment only. Sadly, in this case, the blood film of myeloblasts and erythroblasts suggests the transformation of Hodgkin's lymphoma into acute myeloid leukaemia, a well-recognised complication of Hodgkin's lymphoma chemotherapy with older alkylating agents,

typically 5 to 10 years after treatment. Blast cells have now subsequently infiltrated the bone marrow, resulting in macrocytic anaemia.

#### Question 5 of 29

A 75-year-old male presents following a fall whilst intoxicated. He has sustained a fractured right neck of femur and is admitted under the orthopaedic team. He has a past medical history of liver cirrhosis, ischaemic heart disease and congestive cardiac failure. There is a suspicion that he drinks excessively.

On examination, his right leg is externally rotated and shortened. He is thin and has mild pitting oedema to his mid-shins. His pulse is 92 beats per minute and regular, respiratory rate 18 breaths per minute, blood pressure 121/72 mmHg, SaO<sub>2</sub> 94% on room air. Apart from a slight expiratory wheeze, his chest is clear to auscultation.

Bloods show:

Hb 112 g/l  
Platelets  $48 \times 10^9/l$   
WBC  $11.2 \times 10^9/l$   
INR 1.9

The orthopaedic team arrange for a transfusion of two units of fresh frozen plasma (FFP) and two units of platelets before taking the patient to theatre.

Four hours after the transfusion the patient has become unwell.

Observations show a respiratory rate of 34 breaths per minute, SaO<sub>2</sub> 80% on room air. Heart rate is 120 beats per minute and regular. Temperature is 38.5°C. A chest X-ray is performed at the bedside which shows bilateral shadowing.

What is the most likely cause of the patient's deterioration?

[Community acquired pneumonia5% Transfusion associated circulatory overload21% Acute myocardial infarction4% Transfusion associated acute lung injury66% Atrial fibrillation with a rapid ventricular response4%](#)

The history is not suggestive of a community-acquired pneumonia so this is unlikely.

Transfusion-associated circulatory overload (TACO) is an increasingly recognised complication of transfusion which can result in significant morbidity and even death. Patients aged over 70 are at increased risk of TACO. The concept that one unit of packed red cells leads to a 1g/dL increment only applies to a patient weighing 70-80 kg. As a general guide transfusing, a volume of 4ml/kg typically gives an increment of 1g/dL. TACO can occur anytime within six hours of transfusion. TACO can present with any of the following:

- acute respiratory distress
- tachycardia
- increased blood pressure
- acute or worsening pulmonary oedema

Management of TACO is with diuretics and the haematocrit should be measured. In cases where there has been a dramatic elevation in haematocrit, venesection may be required to reduce the risk of a stroke. Whilst TACO is an important differential, in this case, the patient's symptoms start later than would be expected. In addition, the risk of TACO is higher with packed red cells than with FFP or platelets again making this choice less likely.

Again acute myocardial infarction would be a differential to consider but there is no chest pain in the history to suggest this, so this is not the most likely answer here. Similarly, atrial fibrillation leading to acute left ventricular failure is a differential to consider and an electrocardiogram would be an important investigation but the pulse feels regular in the patient which makes this a less likely diagnosis.

Transfusion-related acute lung injury (TRALI) is the most likely answer in this case. TRALI presents with acute shortness of breath and hypoxia within six hours of transfusion. Bilateral pulmonary infiltrates are seen on chest X-ray and it is often accompanied by a temperature. Whilst uncommon it is the leading cause of transfusion-related mortality. It is caused by human leucocyte antibodies/human neutrophil antibodies from donor plasma. It occurs more commonly with platelets and FFP than with packed red cells. Blood can be sent for serology and anti-leucocyte antibodies are seen in the donor plasma which react with recipient neutrophil antigens. The mainstay of management is supportive care but intubation and ventilation are often required.

## **Blood product transfusion complications**

### Complications

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, vCJD
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

### Immediate haemolytic reaction

- e.g. ABO mismatch

- massive intravascular haemolysis

#### Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions

#### Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

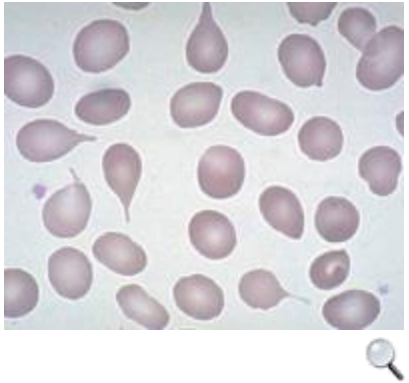
#### Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
- → from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
- → from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
- → from 2004 onward, recipients of blood components have been excluded from donating blood

#### Question 6 of 29

A 77-year-old man is referred to haematology for investigation of anaemia. For several months he has been complaining of fatigue and weight loss. His GP has already arranged upper and lower gastrointestinal (GI) endoscopy which has been reported as normal.

His blood film is shown below:



What is the most likely diagnosis?

[Chronic lymphocytic leukaemia 5%](#)[Myelofibrosis 75%](#)[Iron deficiency anaemia \(bleeding from non-GI source\) 8%](#)[Hyposplenism 9%](#)[Autoimmune hemolytic anaemia 3%](#)

The blood film shows the typical 'tear-drop' poikilocytes of myelofibrosis.

## **Myelofibrosis**

### Overview

- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen

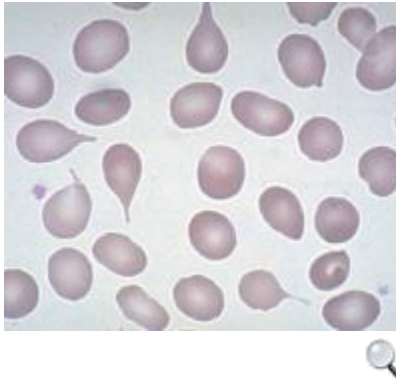
### Features

- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- massive splenomegaly
- hypermetabolic symptoms: weight loss, night sweats etc

### Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film

- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

#### Question 7 of 29

A 24-year-old female presents to the emergency department with severe abdominal pain which had developed over the last few hours. The pain was central, severe and stabbing in nature associated with vomiting. She was in hysterics and was extremely agitated and confused. Past medical history included asthma and depression. Two days earlier she had seen her GP for dysuria and been prescribed trimethoprim.

She was a student studying chemistry at university and had recently been out late several nights drinking excess alcohol to celebrate passing her exams. On examination, she was unwell, extremely clammy, distressed with generalised abdominal tenderness and weakness in both legs with areflexia. Heart sounds and chest were clear. Observations showed a blood pressure 190/100 mmHg, heart rate 126/min, regular and temperature 37.9°C.

Which investigation is most likely to be diagnostic?

[Urinary catecholamines 9%](#) [Abdominal ultrasound 6%](#) [Urinary porphobilinogen 79%](#) [Lumbar puncture 3%](#) [Blood cultures 3%](#)

This patient has acute intermittent porphyria (AIP). AIP is the most common type of porphyria. AIP is an autosomal dominant condition caused by a genetic mutation in the gene encoding the enzyme porphobilinogen (PBG) deaminase on chromosome 11. The condition is more common in females than males and usually occurs between the ages 14-30 years. Porphyrias occur due to a problem within the haem biosynthesis. Defective PBG deaminase causes PBG to accumulate and this can be found in the urine. Attacks are usually precipitated by drugs, alcohol, fasting and sepsis. This patient's attack has been caused by a combination of antibiotic use and alcohol.

intake.

Patients most commonly present with gastrointestinal symptoms (most commonly severe abdominal pain) neurological symptoms (autonomic dysfunction, peripheral motor neuropathies, areflexia, delirium, seizures, coma) and psychiatric symptoms such as common. Observations commonly show tachycardia and hypertension. Fever can be present. Most patients are completely free of symptoms between attacks.

The treatment for acute attacks of porphyria is to decrease haem synthesis and reduce the production of porphyrin precursors. Withdrawal of culprit medication is essential. A high-calorie intake and high doses of glucose can help inhibit haem synthesis and are useful for the treatment of mild attacks. In severe attacks, intravenous haematin is used. Pain is treated with narcotics. Beta blockers can be used to treat tachycardia and hypertension.

Advice can be obtained from National Acute Porphyria Centres: Cardiff, Kings College Hospital, London and Cambridge.

### **Acute intermittent porphyria**

Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

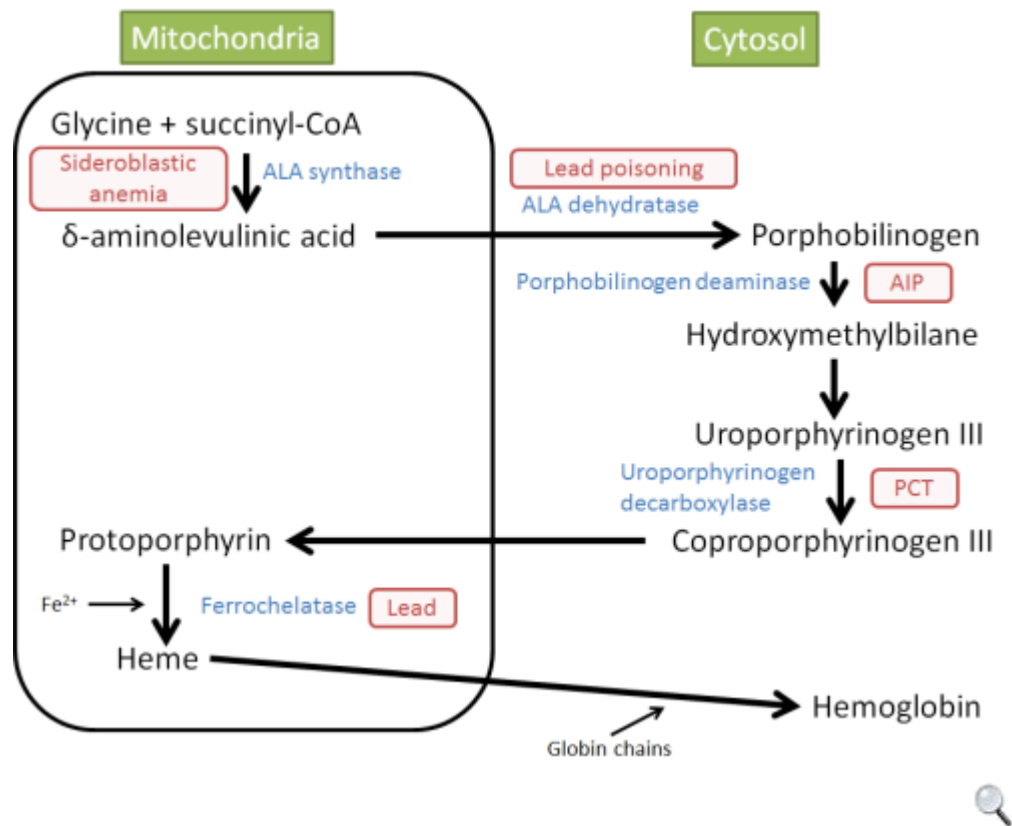
#### **Features**

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

#### **Diagnosis**

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen





#### Question 8 of 29

A 67-year-old female presents with 4-month history of increasing lethargy and malaise. She has no past medical history and travels widely, last visiting the Middle East one week prior to this admission, returning with a respiratory tract infection that appears to be resolving. She is a lifelong non-smoker and does not drink alcohol to excess. Over the past two weeks, she reports increasing bilateral persistent headache associated with binocular visual blurring. In addition, she describes a non-specific abdominal discomfort without any changes in bowel habit.

On examination, you note bilateral axillary lymphadenopathy and conjunctival pallor. Cardiovascular and respiratory system examinations were unremarkable. Neurological examination is unremarkable. Fundoscopy reveals dilated tortuous retinal veins. Abdominal examination reveals hepatosplenomegaly. Lastly, you note areas of purpura around her left anterior shin and her right upper arm. A chest radiograph is unremarkable.

Her blood results are as follows:

Hb	87 g/l
MCV	79 fl

Platelets	190 * 10 <sup>9</sup> /l
WBC	3.4 * 10 <sup>9</sup> /l
Na <sup>+</sup>	142 mmol/l
K <sup>+</sup>	4.5 mmol/l
Urea	7.6 mmol/l
Creatinine	89 µmol/l
Adj Calcium	2.47 mmol/l
Phosphate	1.34 mmol/l
LDH	1890 (normal range 140-280 units/L)
Serum electrophoresis IgM paraprotein band at 5.4 g/L	

A bone marrow biopsy demonstrates 14% infiltration of lymphoplasmacytic cells

What is the most likely diagnosis?

[Waldenstrom's macroglobulinaemia70%Multiple myeloma8%Monoclonal gammopathy of unknown significance \(MGUS\)12%Chronic lymphocytic leukaemia \(CLL\)7%Upper respiratory tract infection \(URTI\)3%](#)

There is an enormous IgM paraprotein band on serum electrophoresis, immediately suggesting the differentials to narrow to Waldenstrom's macroglobulinaemia, multiple myeloma and MGUS. The patient is symptomatic, has bone marrow involvement of greater than 10% with IgM band greater than 3g/L, ruling out MGUS. The key to this diagnosis is differentiating between myeloma and Waldenstrom's: it is particularly rare (but not impossible) for an IgM-secreting plasma cell clone in myeloma but this accounts for only 0.5% of all multiple myelomas. Secondly, clinically, the patient demonstrates signs of hyperviscosity syndrome and splenomegaly, both of which are much more common in Waldenstrom's than myeloma. Thirdly, there is a lack of bone symptoms and renal involvement with normal serum calcium: bone lesions are significantly more common in multiple myeloma. Fourthly, fundoscopic tortuous and dilated veins are classical in hyperviscous patient with Waldenstrom's macroglobulinaemia. The diagnosis is clinched on bone marrow biopsy, demonstrating lymphoplasmacytic cells instead of plasma cells, confirmed by cell immunophenotyping.

CLL should not result in a paraprotein band, URTI may result in a rise in IgA but should not result in bone marrow involvement.

### **Waldenstrom's macroglobulinaemia**

Waldenstrom's macroglobulinaemia is an uncommon condition seen in older men. It is a

lymphoplasmacytoid malignancy characterised by the secretion of a monoclonal IgM paraprotein

#### Features

- monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- hyperviscosity syndrome e.g. visual disturbance
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

#### Question 9 of 29

A 77-year-old lady was seen in the haematology outpatient clinic for her monthly follow-up. She has been seen in the haematology clinic for the last six months having been referred by her GP following an anomaly on her blood investigations. Overall she has been feeling well though for the last three weeks she has been feeling increasingly tired. She has noted that her appetite has been reduced for the last three months though she has not lost any weight during this time. In spite of the tiredness she is still able to lead an active life, regularly enjoying long distance rambling and gardening. She denied the presence of other symptoms, including the absence of fever or night sweats. She has a past medical history comprising asthma, hypertension, type 2 diabetes mellitus and hypercholesterolaemia for which she has been prescribed felodipine 5mg M/R OD, atorvastatin 20mg ON, Clenil modulite 2 puffs BD and metformin 500mg TDS.

Examination revealed the presence of a well elderly lady who was independently mobile. Her blood pressure was 122/82 mmHg, heart rate 82bpm and temperature 36.9 Celsius. Examination of her cardiovascular and respiratory systems revealed the presence of normal heart and breath sounds and a JVP of 3cm. Examination of her gastrointestinal and lymphatic systems revealed the presence of a smooth edge 2 fingerbreadth below the left subcostal margin and bilateral small cervical lymphadenopathy, with the maximum node size less than 1cm.

Investigations reveal the following:

Results from clinic three months ago:

Hb	112 g/l
Platelets	242 * 10 <sup>9</sup> /l
WBC	22.6 * 10 <sup>9</sup> /l
Neutrophils	2.1 * 10 <sup>9</sup> /l
Lymphocytes	19.9 * 10 <sup>9</sup> /l
Eosinophils	0.4 * 10 <sup>9</sup> /l
Monocytes	0.2 * 10 <sup>9</sup> /l

Renal and liver function tests were normal.

Blood film: lymphocytosis with atypical lymphocytes

Bone marrow aspirate: infiltration with 25% lymphocytes

Peripheral blood flow cytometry: presence of circulating clonal B-lymphocytes expressing CD5, CD19, CD20, CD 23, and an absence of FMC-7 staining

Results from clinic on this occasion:

Hb	106 g/l
Platelets	$162 \times 10^9/l$
WBC	$34.2 \times 10^9/l$
Neutrophils	$2.3 \times 10^9/l$
Lymphocytes	$31.5 \times 10^9/l$
Eosinophils	$0.3 \times 10^9/l$
Monocytes	$0.1 \times 10^9/l$

What is the single next best step management step?

[Commence prednisolone therapy5%](#)[Commence chlorambucil therapy13%](#)[Commence fludarabine therapy14%](#)[Commence rituximab therapy13%](#)[Observe in clinic and repeat tests in one month56%](#)

This lady has chronic lymphocytic leukaemia (CLL) as manifested by the high lymphocyte count, lymphocyte marrow infiltration and evidence clinically of splenomegaly and lymphadenopathy. 70% of patients are asymptomatic and patients with stage A leukaemia as with this lady [no anaemia or thrombocytopaenia and less than 3 areas of lymphoid enlargement] have a median survival of 8 years. Treatment is therefore not indicated.

Accepted indications for treatment include:

- The development of anaemia +/- thrombocytopaenia
- Progressive or massive splenomegaly (6cm) +/- lymphadenopathy (10cm)
- Progressive lymphocytosis [50% increase in 2 months or doubling time of less than 6 months]
- Systemic symptoms [fever, night sweats, weight loss >10% in 6 months, extreme fatigue]

Although this lady has been complaining of tiredness, this does not in itself constitute a 'systemic symptom' given the absence of other symptoms and her strong performance status. Her lymphocyte count is rising but does not meet the criteria for treatment at present. Should treatment be indicated, this comprises chemotherapeutic agents such as chlorambucil and fludarabine, immunological agents such as rituximab and steroids in advanced disease.

## Chronic lymphocytic leukaemia: management

### Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopenias e.g. ITP

### Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

### Question 10 of 29

A 64-year-old female undergoing chemotherapy treatment with mitomycin for bladder cancer presents to the Emergency Department with confusion, epistaxis and a widespread rash. On examination, she is febrile and has a diffuse petechial rash.

Hb	10.6g/dl
Platelets	$54 \times 10^9/l$
WBC	$11.2 \times 10^9/l$
Urea	11mmol/l
Creatinine	117 $\mu$ mol/l
Bilirubin	58 $\mu$ mol/l
ALP	42u/l

A blood film shows fragmented erythrocytes.

What is the most appropriate treatment for this patient?

[Renal dialysis5%Supportive treatment14%A pool of platelets and fluid resuscitation8%Urgent plasma exchange59%IV tazocin, a pool of platelets and fluid resuscitation14%](#)

Thrombotic thrombocytopenic purpura (TTP) is characterised by fluctuating neurological signs, fever, renal dysfunction, microangiopathic haemolysis and thrombocytopenia. The key to diagnosis is differentiating between TTP and haemolytic-uraemic syndrome (HUS). The presence of neurological signs in TTP and more severe renal dysfunction in HUS usually helps in distinguishing the two.

Congenital TTP is caused by a deficiency in von Willebrand factor. However, the majority of cases are secondary and can occur in pregnancy, HIV and associated with some drugs. In particular, the chemotherapeutic agents mitomycin C, bleomycin, tamoxifen and gemcitabine are all associated with secondary TTP. Other drugs in association include penicillin, rifampicin and immunosuppressive drugs eg. ciclosporin A.

The standard treatment for TTP is IV plasma exchange which should be initiated as soon as possible.

### **Thrombotic thrombocytopenic purpura: management**

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

### Question 1 of 19

A 55-year-old lady presents to her general practitioner with a painful rash on her breasts. The rash has developed over the last 24 hours and although initially diffuse and red is now well demarcated and a much darker red. She was started on warfarin five days ago for a deep vein thrombosis diagnosed on ultrasound doppler. She has a past medical history of hypothyroidism, type two diabetes mellitus, thromboembolism and obesity. She remembers having been on warfarin at least once before for previous deep vein thrombosis but does not remember ever having had this rash. Her blood tests today are as follows.

Prothrombin time 21.4 seconds

INR 2.1 ratio

What is the most likely diagnosis?

[Protein S deficiency12%](#)[Idiosyncratic drug reaction22%](#)[Stevens Johnson syndrome8%](#)[Warfarin toxicity8%](#)[Protein C deficiency50%](#)

Warfarin-induced skin necrosis is a symptom of the hypercoagulable state that can be seen in the first week of warfarin therapy. This is explained by the fact that warfarin inhibits both pro-coagulant factors (2, 7, 9, 10) as well as anti-coagulant factors (protein C). Protein C has the shortest half-life and therefore there is a short period of time during the initiation of warfarin therapy where the patient is hypercoagulable despite a therapeutic INR. Warfarin-induced skin necrosis is more likely to occur in patients with pre-existing protein C deficiency, which is a rare congenital condition associated with recurrent venous thromboembolic disease.

### Protein C deficiency

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis

#### Features

- venous thromboembolism
- skin necrosis following the commencement of warfarin: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis

### Question 2 of 19

A 32-year-old patient who is 10 weeks pregnant attends for her antenatal booking clinic. This is her first pregnancy, and she tells you she has been feeling lethargic and has a poor appetite. She has no past medical history of note.

On examination, she looks pale and appears comfortable at rest. Her chest is clear, heart sounds I&II are present and her abdomen is soft non-tender. She has some oedema of both ankles bilaterally. Her blood pressure is 111/75 mmHg and her heart rate is 79/min.

Investigations in clinics are as follows:

Hb	94 g/l
MCV	69 fl
Platelets	$168 \times 10^9/l$
WBC	$9.1 \times 10^9/l$
Hb electrophoresis	positive HbA2
Rhesus	negative
Blood Group	AB

Na <sup>+</sup>	139 mmol/l
K <sup>+</sup>	3.9 mmol/l
Urea	7.6 mmol/l
Creatinine	99 $\mu$ mol/l

What is the single most likely underlying condition?

[Alpha thalassaemia trait19%Beta thalassaemia trait62%Beta thalassema major8%Iron deficiency anaemia7%Sideroblastic anaemia4%](#)

The two main differentials in this patient who has been identified as having a symptomatic microcytic anaemia during pregnancy are iron deficiency anaemia and beta thalassaemia trait. The clue that this is beta thalassaemia trait rather than iron deficiency anaemia is that the MCV is surprisingly low for the level of haemoglobin. In iron deficiency anaemia you would expect the MCV to be much higher for a fairly modest decrease in haemoglobin.

In addition, the Hb electrophoresis shows +ve HbA2 which supports the diagnosis of beta thalassaemia trait. Of course, it would be wise to send off iron studies in this patient to assess for a coexistent iron deficiency anaemia.



## Beta-thalassaemia trait

The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. Beta-thalassaemia trait is an autosomal recessive condition characterised by a mild hypochromic, microcytic anaemia. It is usually asymptomatic

### Features

- mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia
- HbA2 raised ( $> 3.5\%$ )

### Question 4 of 19

A 30-year-old woman with a background of systemic lupus erythematosus presents to the emergency department with fatigue and poor urine output.

On examination, she is jaundiced, with a petechial rash affecting her lower limbs which is non-tender to palpation. She is afebrile, mildly tachycardiac with a heart rate of 95/min and is normotensive.

### Bloods:

Hb	50 g/l	Na <sup>+</sup>	135 mmol/l
Platelets	$30 \times 10^9/l$	K <sup>+</sup>	4.9 mmol/l
WBC	$11 \times 10^9/l$	Urea	6 mmol/l
Neuts	$6 \times 10^9/l$	Creatinine	300 $\mu\text{mol/l}$
Lymphs	$3 \times 10^9/l$	CRP	25 mg/l
Eosin	$0 \times 10^9/l$		

What is the most appropriate definitive management?

[Transfusion of packed red cells6% Intravenous fluids3% Rituximab4% Pulsed methylprednisolone33% Plasma exchange53%](#)

Thrombotic thrombocytopenic purpura

Pathogenesis of thrombotic thrombocytopenic purpura (TTP):

- Abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels

in TTP there is a deficiency of ADAMTS13 (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor. There is an overlap between TTP and HUS, with the common consensus being that they are a continuum of disease.

Features - classic 'pentad'

1. MAHA
2. Low platelets
3. fever
4. fluctuating neuro signs (microemboli)
5. AKI

- Classic 'pentad' very rarely seen since the advent of plasma exchange
- Mortality up to 90% if untreated, and 20% with plasma exchange

Causes:

- Post-infection e.g. urinary, gastrointestinal
- Pregnancy
- Drugs: ciclosporin, oral contraceptive pill, penicillin, clopidogrel, aciclovir
- Tumours
- SLE
- HIV
- Idiopathic

Thrombotic thrombocytopenic purpura: management

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- In TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- Overlaps with the haemolytic-uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants

- vincristine

New therapies - such as eculizumab (a monoclonal antibody targeting terminal commitment pathway C5)

## **Thrombotic thrombocytopenic purpura: management**

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

Question 5 of 19

A 34-year-old male was admitted after being found on the floor. He admitted to drinking too much alcohol, and had taken cannabis and inhaled nitrate based poppers' with his friends. He is a long term heavy smoker, and was admitted before with alcohol toxicity and other illicit drug use but does not have other past medical history. He was admitted to the Acute Medical Unit because his saturations were only 88- 90% on 10L of oxygen despite being asymptomatic. He had a heart rate of 90 beats/min, blood pressure of 118/80 mmHg, respiratory rate of 14/min and was noticed to have peripheral cyanosis. On auscultation, there was very mild scattered wheeze, but otherwise good air entry. The arterial blood gas on air revealed the following:

pH      7.36  
pCO<sub>2</sub>   5.8 kPa

pO<sub>2</sub> 10.8 kPa  
HCO<sub>3</sub><sup>-</sup> 22 mmol/l  
BE -2.4 mmol/l  
Sats 90%  
MetHb 16%  
Na 136 mmol/l  
K 4.6 mmol/l  
Lactate 1.8 mmol/l

What is the most appropriate management?

Reduce oxygen from high flow to 28% via venturi mask7% Nebulised salbutamol4% Methylene blue78% Start non-invasive ventilation5% Desferrioxamine6%

Methaemoglobin is an altered state of haemoglobin in which the ferrous (Fe<sup>2+</sup>) irons of heme are oxidised to the ferric (Fe<sup>3+</sup>) state. The ferric haemes of methaemoglobin are unable to bind oxygen. Normal levels are <1.5%

There are congenital and acquired causes ( nitrates/nitrite compounds such as amyl nitrates and glyceryl trinitrates, local anaesthetic, benzene derivatives, sulphonamides)  
Treatment is with methylene blue, supportive care and monitoring.

Option 1: Patient should remain on high concentration of oxygen

Option 2: Although the patient is a heavy smoker and has mild wheeze on examination, chronic obstructive pulmonary disease would not explain the ABG results

Option 4: no indication for Desferrioxamine

Option 5: is the antidote for ferrous poisoning.

## **Methaemoglobinaemia**

Methaemoglobinaemia describes haemoglobin which has been oxidised from Fe<sup>2+</sup> to Fe<sup>3+</sup>. This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as Fe<sup>3+</sup> cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

## Acquired causes

- drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

## Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal pO<sub>2</sub> but decreased oxygen saturation

## Management

- NADH - methaemoglobinemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

## Question 6 of 19

A 69-year-old gentleman presented for routine follow-up in the oncology clinic. He has metastatic poorly differentiated adenocarcinoma of unknown primary. He commenced palliative chemotherapy with oxaliplatin and fluorouracil two months ago. The most recent CT scan demonstrated stable disease.

Ten days ago he was admitted to the local emergency department with fever and diagnosed with neutropenic sepsis, of which the cause was not clear. He was admitted for IV Tazocin for five days then discharged with co-amoxiclav and filgrastim (G-CSF). He currently feels well. On examination there are no abnormalities.

### Observations:

Saturations 95%

Respiratory rate 14/min

Blood pressure 152/83mmHg

Heart rate 69/min

Temperature 37.3°C

### Blood tests:

Date 24/10/2016 10/10/2016

Hb 124g/l 135g/l  
Platelets  $285 \times 10^9/l$   $322 \times 10^9/l$   
WBC  $23.6 \times 10^9/l$   $0.2 \times 10^9/l$

What is the most appropriate course of action?

[Restart oral co-amoxiclav4%Arrange admission for IV tazocin6%Arrange admission for IV meropenem7%Start prednisolone6%Stop filgrastim \(G-CSF\)76%](#)

The correct answer is to stop filgrastim. Filgrastim stimulates a white cell count which can increase far above the normal range, and the white cell count will return to normal once it is stopped. The key here is that the patient is clinically well, and further antibiotics are unnecessary.

Source:

Febrile Neutropenia.' BMJ Best Practice. N.p., 15 Sept. 2015.

## Neutropenic sepsis

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy. It may be defined as a neutrophil count of  $< 0.5 \times 10^9$  in a patient who is having anticancer treatment and has one of the following:

- a temperature higher than  $38^\circ\text{C}$  or
- other signs or symptoms consistent with clinically significant sepsis

## Prophylaxis

- if it is anticipated that patients are likely to have a neutrophil count of  $< 0.5 \times 10^9$  as a consequence of their treatment they should be offered a fluoroquinolone

## Management

- antibiotics must be started immediately, do not wait for the WBC
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment

- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

#### Question 8 of 19

A 23-year-old man presents to the emergency department acutely unwell for the last 72 hours. He has been fatigued for the last month and has been having night sweats and has had several colds. Over the last 3 days, he has become more unwell, shivery and vomiting. He has noticed bruising on forearms and thighs. On examination, he is drowsy and has a temperature of 38.5°C. His blood pressure is 90/50 mmHg, heart rate 120/min. He is peripherally shut down with a cap refill time of 5 seconds. He has conjunctival pallor. He is given IV fluids and antibiotics by the emergency department. His blood results show:

Hb	89 g/l
Platelets	43 * 10 <sup>9</sup> /l
WBC	13.0 * 10 <sup>9</sup> /l
Neutrophils	9.0 * 10 <sup>9</sup> /l
D-Dimer	5.8mg/L (<0.5)
INR	8.5
PT	89 seconds (9-12)
APTT ratio	1.7 (0.8-1.2)
Fibrinogen	0.1g/L (1.5 - 4.5)
Blood film	Faggot cells seen

Na <sup>+</sup>	138 mmol/l
K <sup>+</sup>	5.8 mmol/l
Urea	18 mmol/l
Creatinine	195 µmol/l
CRP	170 mg/l

Bilirubin	8 µmol/l
ALP	102 u/l
ALT	300 u/l
Albumin	38 g/l

He is transferred to ITU for ionotropic support. He is treated with fresh frozen plasma which corrects his coagulopathy. Haematology is involved and he has a bone marrow analysis performed. Cytogenetics shows a translocation of chromosomes 15 and 17. What is the appropriate treatment to give?

[All-trans retinoic acid 58% R-CHOP 19% Chlorambucil 10% High dose prednisolone 8% Ribavirin 5%](#)

This patient has acute promyelocytic leukaemia (M3 subclass). This can present with DIC in young patients the prolonged prothrombin time, with platelets consumption and low fibrinogen. Faggot cells are hypergranular promyelocytes, so called because the high concentrations of Auer rods in the cytoplasm give the cells a bundle of sticks appearance. The gene translocation of 15:17 results in a fusion gene of PML:RARA (retinoic acid receptor). The exact process by which this gene fusion results in AML is unclear but the condition responds well to retinoic acid therapy hence this is the correct answer here. The other options are for other types of haematological malignancy.

### **Acute promyelocytic leukaemia**

You are not normally expected to be able to differentiate the different subtypes of acute myeloid leukaemia (AML) for the MRCP. An exception to this is acute promyelocytic leukaemia (APML, the M3 subtype of AML). The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management

APML is associated with the t(15;17) translocation which causes fusion of the PML and RAR-alpha genes.

#### **Features**

- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- good prognosis



### Question 9 of 19

A 77-year-old female is referred to the hospitals ambulatory care clinic by her GP after 2 months of increasing generalised malaise and 'lack of energy' over the past two months. She lives with her husband and until 9 weeks ago, continued to drive and go for walks in the countryside with no limitations to her exercise tolerance. Now, she feels 'tired all the time' but denies any problems with her mood. She has no history of psychiatric disorders. Her past medical history includes hypertension (well controlled on ramipril alone), hypercholesterolaemia (well controlled on simvastatin) and chronic lymphocytic leukaemia, diagnosed 3 years ago and not requiring treatment.

On examination, she has warm peripheries with bilateral conjunctival pallor. She is alert and comfortable at rest. Non-tender lymphadenopathy in bilateral cervical chains. Her cardiovascular, respiratory, abdominal and neurological examinations are otherwise unremarkable. Her blood results are as follows:

Hb	72 g/l
MCV	101 fl
Platelets	$70 \times 10^9/l$
WBC	$67.0 \times 10^9/l$
Neut	$4.0 \times 10^9/l$
WBC	$62.0 \times 10^9/l$
Reticulocytes	14%
Blood film and direct agglutination test	lymphocytosis, smudge cells, reticulocytes, red cell agglutination at physiological temperature

What is the most likely cause of this patient's anaemia?

[Cold autoimmune haemolytic anaemia16%](#) [Warm autoimmune haemolytic anaemia63%](#) [B12 deficiency anaemia7%](#) [Iron deficiency anaemia5%](#) [Microangiopathic haemolytic anaemia9%](#)

The patient presents with a borderline macrocytic/normocytic anaemia with a positive Coombs test at 37 degree temperature, suggesting an autoimmune haemolytic anaemia. The presence of red cell agglutination at a warm temperature suggests the presence of IgG on red blood cells, which in vivo leads to phagocytosis by a granulocyte: this is warm autoimmune haemolytic anaemia. Conversely, red cell agglutination at cold temperatures, typically between 0 and 4 degrees, suggests the presence of IgM and C3 component of complement, most commonly leading to direct cell lysis by the complement system: this is cold autoimmune haemolytic anaemia. A mildly raised or borderline MCV does not necessarily guarantee a macrocytic cause in this context: the high proportion of reticulocytes in the blood demonstrates increased red cell production from marrow, increasing the release of immature cells with higher corpuscular volume than mature red cells, hence the increased MCV in blood assays. Iron deficiency anaemias typically produce microcytic anaemias with target cells. Microangiopathic haemolytic anaemia (MAHA) is caused by the mechanical destruction of red cells in conditions such as thrombotic thrombocytopenic purpura, leading to fragmented red cells (schistocytes) and a

typically normocytic picture with associated thrombocytopenia.

Both warm and cold autoimmune haemolytic anaemias can be idiopathic or caused by lymphoproliferative disorders. Warm agglutinins are also more commonly produced by systemic autoimmune conditions such as SLE, rheumatoid arthritis and systemic sclerosis, while cold agglutinins are also classically triggered by mycoplasma and viral infections such as infectious mononucleosis.

## **Autoimmune haemolytic anaemia**

Autoimmune haemolytic anaemia (AIHA) may be divided into 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis. It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs. AIHA is characterised by a positive direct antiglobulin test (Coombs' test)

### **Warm AIHA**

In warm AIHA the antibody (usually IgG) causes haemolysis best at body temperature and haemolysis tends to occur in extravascular sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy

Causes of warm AIHA

- autoimmune disease: e.g. systemic lupus erythematosus\*
- neoplasia: e.g. lymphoma, CLL
- drugs: e.g. methyl dopa

### **Cold AIHA**

The antibody in cold AIHA is usually IgM and causes haemolysis best at 4 deg C. Haemolysis is mediated by complement and is more commonly intravascular. Features may include symptoms of Raynaud's and acrocyanosis. Patients respond less well to steroids

Causes of cold AIHA

- neoplasia: e.g. lymphoma
- infections: e.g. mycoplasma, EBV

\*systemic lupus erythematosus can rarely be associated with a mixed-type autoimmune haemolytic anaemia

#### Question 13 of 19

A 60-year-old female with known chronic lymphocytic leukaemia (CLL) presents with coryzal symptoms. Examination findings are unremarkable. Her blood tests are as follows:

	8 months previously	Two months previously	Today
Haemoglobin	113 g/l	108 g/l	106 g/l
White cell count	$32.0 \times 10^9/l$	$50.0 \times 10^9/l$	$58.0 \times 10^9/l$
Neutrophils	$7.0 \times 10^9/l$	$4.8 \times 10^9/l$	$4.0 \times 10^9/l$
Lymphocytes	$25.0 \times 10^9/l$	$45.0 \times 10^9/l$	$54.0 \times 10^9/l$
Platelets	$358 \times 10^9/l$	$280 \times 10^9/l$	$268 \times 10^9/l$

What is the most appropriate treatment option?

[Chlorambucil6%Fludarabine and chlorambucil25%Observation59%Prednisolone3%Fludarabine6%](#)

CLL is typically an indolent disease which is often managed conservatively in the first instance. Indications for treatment are multiple but include constitutional symptoms, bone marrow failure and massive lymphadenopathy. Additionally, a lymphocyte doubling time of less than 6 months is an indication for treatment, but this is not met here. Chlorambucil, fludarabine and high dose corticosteroids are all possible therapeutic options in CLL.

### Chronic lymphocytic leukaemia: management

#### Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months

- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopenias e.g. ITP

## Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

## Question 15 of 19

A 23-year-old female has presented with her first episode of seizure on the labour ward, 2 days after delivering her first child by normal vaginal delivery. She reports a fluctuating generalised headache over the past 3 months but had not previously sought medical attention. In addition, she had spiked 2 fevers over 38°C over the past 48 hours, with no dysuria, diarrhoea or vomiting, productive cough or signs of meningism. She has no past medical history, is a life-long non-smoker and has been abstinent from alcohol for 9 months, previously drinking 4 units per week. Her seizure was witnessed and described as tonic-clonic jerking of all 4 limbs, associated with loss of consciousness, terminated after 4mg of intravenous lorazepam after 4 minutes. On examination, she appears post-ictal but responding to voice despite being sleepy. Pupils are reactive and equal. Plantars are downgoing bilaterally. Cardiovascular, abdominal and respiratory examinations are unremarkable. No skin rashes, neck stiffness or photophobia are noted. Her blood results are as follows:

Hb	75 g/l
MCV	87 fl
Platelets	$23 \times 10^9/l$
WBC	$9.2 \times 10^9/l$
Blood film	schistocytes
Coombs' test	negative
CRP	30 mg/l
Urea	12.6 mmol/l
Creatinine	154 $\mu$ mol/l
Bilirubin	28 $\mu$ mol/l
ALP	98 u/l
ALT	28 u/l
$\gamma$ GT	23 u/l

A CT head with contrast demonstrated no areas of ischaemia, haemorrhage or space occupying lesion.

Which is the next most appropriate immediate management?

[Plasma exchange](#)67% [Intravenous 3rd generation cephalosporin antibiotics](#)7% [Intravenous phenytoin loading](#)8% [MRI head with contrast](#)8% [Intravenous steroids](#)10%

This young lady's blood tests demonstrated a normocytic anaemia associated with schistocytes (fragmented red cells) with negative Coombs' test, suggestive of mechanical destruction of red cells. In addition, thrombocytopenia is present with renal impairment and normal liver function tests. The initial presentation is of first seizure and fluctuating headache, with two unexplained fevers. The pentad of fever, fluctuating neurological symptoms, microangiopathic haemolytic anaemia, thrombocytopenia and renal impairment represents thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome spectrum (TTP-HUS), resulting in microvascular thrombus formation. There is little to suggest an underlying epilepsy syndrome and no indication for phenytoin loading after a single seizure without status epilepticus. While meningitis may cause headaches, a fluctuating 3-month history without meningism is unlikely.

Immediate treatment of TTP-HUS is reliant on plasma exchange without delay in order to remove the high-molecular weight von-Willebrand factor (vWF) driving platelet aggregation and replacing ADAMTS-13 protease, a cleavage enzyme of high molecular weight vWF often deficient in TTP patients, resulting in microvascular thrombi formation. High dose steroids may be appropriate in the setting of refractory disease despite plasma exchange but is an adjunct to plasma exchange, not in place of. Persistent recurrent or refractory TTP-HUS despite plasma exchange and steroids should be considered for the addition of rituximab or increased frequency of plasma exchange. TTP-HUS is a medical emergency and invariably results in death secondary to progressive renal failure if not treated immediately.

## **Thrombotic thrombocytopenic purpura: management**

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

#### Question 16 of 19

A 21-year-old girl complains of easy bruising. She has menorrhagia for which she is being investigated by the gynaecology team. She takes no regular medications. Her father had prolonged bleeding after a tooth extraction.

Blood tests show:

Hb 110 g/L  
 MCV 74 fL  
 WBC  $4.2 \times 10^9/L$   
 Platelets  $135 \times 10^9/L$   
 APTT 1.4  
 INR 1.0

What is the most likely diagnosis?

[Haemophilia B 8%](#) [Anti-thrombin III deficiency 7%](#) [Von Willebrand's disease 65%](#) [Immune thrombocytopenia 7%](#) [Haemophilia A carrier 12%](#)

Von-Willebrand's disease is an autosomal dominant condition (chromosome 12) that leads to a mild-moderate bleeding tendency. The prevalence of clinically significant cases is 1 in 10,000. Factor VIII is bound to vWF, which protects it from breakdown, so deficiency of vWF can lead to low factor VIII levels and a prolonged APTT. In this case the patient also has a microcytic anaemia, which would be in keeping with iron deficiency anaemia secondary to menorrhagia. Haemophilia B (Factor IX deficiency) is X-linked so does not affect females. Haemophilia A (Factor VIII deficiency) is also X-linked. Most carriers are asymptomatic. The APTT is normal in ITP. Anti thrombin III deficiency is a pro thrombotic condition.

#### Von Willebrand's disease

Von Willebrand's disease is the most common inherited bleeding disorder. The majority of cases are inherited in an autosomal dominant fashion\* and characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemarthroses and muscle haematomas are rare

#### Role of von Willebrand factor

- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

#### Types

- type 1: partial reduction in vWF (80% of patients)
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive)

#### Investigation

- prolonged bleeding time
- APTT may be prolonged
- factor VIII levels may be moderately reduced
- defective platelet aggregation with ristocetin

#### Management

- tranexamic acid for mild bleeding
- desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells
- factor VIII concentrate

\*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

A 50-year-old male patient presents with symptoms of unilateral leg swelling. Despite having no predisposing factors for a DVT in his history he is diagnosed as having an above knee thrombosis on Doppler ultrasound. Low molecular weight heparin is started at a treatment dose.

Given the information above what is/are the next most important investigations?

[CTPA9% Thrombophilia screen35% Chest X-ray and urinalysis49% CT head3% Thyroid and liver function tests5%](#)

An unprovoked VTE event requires further investigation. In many regards, it must be treated as malignancy until proven otherwise. Therefore the most simple investigations above to identify malignancy are the most appropriate. A CTPA adds very little as we know the patient has had a VTE event and treatment would not change if a PE was found.

NICE guidance (see link below) on unprovoked VTE event suggests investigating for an underlying malignancy in all patient groups. This should be done with a full history and physical examination, with a chest x-ray, blood tests including calcium levels and liver function, and a urinalysis. The working group also suggest an abdominopelvic CT scan (+ a mammogram in women) for all patients over 40 years of age with a first unprovoked VTE and in whom no malignancy was determined in the initial tests.

NICE guidelines -<http://publications.nice.org.uk/venous-thromboembolic-diseases-the-management-of-venous-thromboembolic-diseases-and-the-role-of-cg144/guidance#investigations-for-cancer-2>



### Question 1 of 295

An 84-year-old male presents as a blue light ambulance call with a twelve hour history of sudden onset inability to move his right side. On examination, you note an expressive and receptive dysphasia associated with a dense right sensori-motor syndrome. Cardiovascular examination was unremarkable except for an irregular heartbeat at 80 per minute. A hyperacute CT head demonstrated a large area of ischaemia in the left middle cerebral artery vascular territory. The patient was outside the window for thrombolysis and started on 300mg aspirin. Subsequent echocardiogram demonstrated 60% ejection fraction with no mural thrombus, 40% left and 35% right stenosis on carotid Doppler while a 24hr tape demonstrated new atrial fibrillation. How can the risk of subsequent strokes be reduced?

[Subcutaneous low molecular heparin at 48 hours after stroke](#)7% [Warfarinisation at 48 hours after stroke](#)6% [Warfarinisation at 14 days after stroke](#)78% [Referral to vascular surgery for left carotid endarectomy](#)4% [Insertion of permanent pacemaker](#)5%

This patient demonstrates an ischaemic infarct secondary to likely new atrial fibrillation, for which the optimum treatment is anticoagulation. The degree of carotid stenosis is not sufficiently significant to justify carotid endarectomy. The patient has no indications for a pacemaker. The treatment of choice for atrial fibrillation in such a high-risk patient for further strokes is anticoagulation.

In the absence of intracerebral haemorrhages or haemorrhagic transformation of infarcts, NICE guidelines recommend starting anticoagulation at 14 days after the onset of stroke<sup>1</sup>. Due to the risk of haemorrhage as the infarcted brain matures, which is increased with the size of the initial infarct, early anticoagulation is not recommended. A recent meta-analysis collated the results of seven trials studying early anticoagulation in acute ischaemic strokes. Although the risk of further ischaemic strokes between days 7 and 14 is significantly reduced from 4.9 to 3%, the risk of symptomatic intracerebral haemorrhage was also significantly increased from 0.7% to 2.5%<sup>2</sup>. As a result, early anticoagulation before 14 days is not indicated by NICE or the American Heart and Stroke Associations<sup>3</sup>.

1. Atrial Fibrillation: the management of atrial fibrillation. NICE Guideline 2006

2. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2007;38(2):423

3. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870.

## Stroke: management

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is  $> 3.5$  mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

Absolute	Relative
<ul style="list-style-type: none"><li>- Previous intracranial haemorrhage</li><li>- Seizure at onset of stroke</li><li>- Intracranial neoplasm</li><li>- Suspected subarachnoid haemorrhage</li><li>- Stroke or traumatic brain injury in preceding 3 months</li><li>- Lumbar puncture in preceding 7 days</li><li>- Gastrointestinal haemorrhage in preceding 3 weeks</li><li>- Active bleeding</li></ul>	<ul style="list-style-type: none"><li>- Concurrent anticoagulation (INR <math>&gt;1.7</math>)</li><li>- Haemorrhagic diathesis</li><li>- Active diabetic haemorrhagic retinopathy</li><li>- Suspected intracardiac thrombus</li><li>- Major surgery / trauma in preceding 2 weeks</li></ul>

## Absolute

## Relative

- Pregnancy
- Oesophageal varices
- Uncontrolled hypertension >200/120mmHg

## Secondary prevention

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

Question 2 of 295

A patient with refractory focal epilepsy on two agents is commenced on levetiracetam in addition. Which adverse effect should patients that have been commenced on this drug most importantly be warned about?

[Oral hairy leukoplakia12%](#) [Weight gain26%](#) [Irritability and aggression36%](#) [QT-interval prolongation17%](#) [Nystagmus10%](#)

It is important to recognise and know something about levetiracetam as it is increasingly becoming a favourite for neurologists to use these days, not least because of its favourable adverse effects profile (wherein it hardly has any compared to many others), but also its ease of use given that you do not need to monitor levels, and its oral and IV bioavailability are the same (useful in nil by mouth patients). It is also recently more affordable having now lost its patent. The one thing to watch out (and ensure you warn patients about) with levetiracetam is behavioural abnormalities and psychotic symptoms. These range from irritability to frank aggression. If there is a background of psychotic symptoms you may wish to avoid levetiracetam. It is something not to miss in the drug history of an epileptic patient who presents to the acute take with a change in behaviour.

1) Mbizvo GK, Dixon P, Hutton JL, Marson AG. The adverse effects profile of levetiracetam in epilepsy: a more detailed look. *The International journal of neuroscience*. 2014 Sep;124(9):627-34. PubMed PMID: 24256446.

2) Mbizvo GK, Dixon P, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review. *The Cochrane database of systematic reviews*. 2012;9:CD001901. PubMed PMID: 22972056.

## **Epilepsy: treatment**

Most neurologists now start antiepileptics following a second epileptic seizure. NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:

- the patient has a neurological deficit
- brain imaging shows a structural abnormality
- the EEG shows unequivocal epileptic activity
- the patient or their family or carers consider the risk of having a further seizure unacceptable

Sodium valproate is considered the first line treatment for patients with generalised seizures with carbamazepine used for partial seizures

Generalised tonic-clonic seizures

- sodium valproate
- second line: lamotrigine, carbamazepine

Absence seizures\* (Petit mal)

- sodium valproate or ethosuximide
- sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy

#### Myoclonic seizures

- sodium valproate
- second line: clonazepam, lamotrigine

#### Focal\*\* seizures

- carbamazepine or lamotrigine
- second line: levetiracetam, oxcarbazepine or sodium valproate

\*carbamazepine may actually exacerbate absence seizure

\*\* the preferred term for partial seizures

#### Question 3 of 295

An 84-year-old male is reviewed in clinic after a 7-month history of progressive confusion, unsteadiness on his feet and new urinary incontinence. He had previously minimal past medical history and continued to volunteer at his local charity shop, taking ramipril alone for hypertension. On examination, his abbreviated mental test score was 2/10, his gait was wide based and ataxic. A mini-mental state examination scores 17/30. His urine dip demonstrated no positive findings and serum results were unremarkable. Although there has been no history of head trauma, a CT head was performed, demonstrated no acute haemorrhages or infarcts. A subsequent MRI demonstrated large ventricles with periventricular white matter changes. Lumbar puncture demonstrated acellular cerebrospinal fluid with no organism growth. Opening pressure was 16 cm H<sub>2</sub>O. You arrange a CSF infusion test, demonstrating raised CSF outflow resistance. Which treatment is most appropriate?

[Therapeutic repeat lumbar punctures9% Ventriculoperitoneal shunt69% Donepezil6% Acetazolamide11% Aspirin 300mg4%](#)

The history and examination are consistent with normal pressure hydrocephalus, with the triad of new onset dementia, urinary incontinence and gait disturbance. The key points in the investigations indicate the suitability of the patient for a ventriculoperitoneal shunt: the raised CSF resistance on CSF infusion test indicates impaired CSF absorption and correlates towards

surgical improvement. In addition, prominent gait disturbance also points towards an increased likelihood of surgical success.

### **Normal pressure hydrocephalus**

Normal pressure hydrocephalus is a reversible cause of dementia seen in elderly patients. It is thought to be secondary to reduced CSF absorption at the arachnoid villi. These changes may be secondary to head injury, subarachnoid haemorrhage or meningitis.

A classical triad of features is seen

- urinary incontinence
- dementia and bradyphrenia
- gait abnormality (may be similar to Parkinson's disease)

It is thought around 60% of patients will have all 3 features at the time of diagnosis. Symptoms typically develop over a few months.

### **Imaging**

- hydrocephalus with an enlarged fourth ventricle
- in addition to the ventriculomegaly there is typically an absence of substantial sulcal atrophy

### **Management**

- ventriculoperitoneal shunting
- around 10% of patients who have shunts experience significant complications such as seizures, infection and intracerebral haemorrhages

### **Question 4 of 295**

A 78-year-old man with a history of atrial fibrillation, diabetes, hypertension and peripheral neuropathy was referred to the anticoagulation clinic by his General Practitioner due to difficulty

controlling the international normalised ratio (INR). He is currently on 12 mg of warfarin and the dose had to be repeatedly increased as his INR has been in the subtherapeutic range in the last month.

Which one of the following medication may be responsible for the above?

[Omeprazole11%Carbamazepine49%Cimetidine11%Valproate15%Ciprofloxacin14%](#)

Carbamazepine is a hepatic enzyme inducer and may reduce the effectiveness of warfarin, whereas the others are enzyme inhibitors.

Others to remember are:

**P450 enzyme inducers P450 enzyme inhibitors**

Phenytoin	Amiodarone
Rifampicin	Ketoconazole
Alcohol	Erythromycin
	Isoniazid
	Sulphonamides
	Allopurinol

**Carbamazepine**

Carbamazepine is chemically similar to the tricyclic antidepressant drugs. It is most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication. Other uses include

- neuropathic pain (e.g. trigeminal neuralgia, diabetic neuropathy)
- bipolar disorder

Mechanism of action

- binds to sodium channels increases their refractory period

Adverse effects

- P450 enzyme inducer

- dizziness and ataxia
- drowsiness
- headache
- visual disturbances (especially diplopia)
- Steven-Johnson syndrome
- leucopenia and agranulocytosis
- syndrome of inappropriate ADH secretion

#### Question 5 of 295

A 58 year old man progressively develops hand clumsiness, gait difficulty and dysphagia over several months. His voice has also become high pitched and nasal. Sensory examination has remained normal throughout. Plantars are up-going, with absent ankle reflexes bilaterally and wasting of the distal leg musculature. Which treatment has been shown to lengthen survival for the underlying condition?

[Intravenous immunoglobulin 14%](#) [Donepezil 10%](#) [Pyridostigmine 9%](#) [Non-invasive ventilation \(NIV\) 59%](#) [Steroids 8%](#)

The answer here is motor neurone disease (specifically Amyotrophic Lateral Sclerosis (ALS) in this case). There is mixture of diffuse upper motor neurone features (the up-going planters and pseudo-bulbar 'Donald duck' speech) along with lower motor neurone features (wasting and areflexia) . The giveaway that it is not other causes of mixed upper and lower motor neurone features e.g. cervical spine pathology/syringomyelia/conus medullaris lesion is the bulbar involvement.

NB: Always look for the presence of tongue fasciculations if you pick up a mixed upper and lower motor neurone picture. If they are evident, think ALS rather than these other causes as they are too low down anatomically to involve the tongue (and bulbar muscles).

Management of ALS involves an multidisciplinary team (MDT) approach. Don't forget to organised Speech and Language Team (SALT) assessment: poor swallow and aspiration pneumonia can kill. Additionally, NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of Forced Vital Capacity (FVC) decline. It has been shown to increase survival by around 205 days. Riluzole has been shown to slow disease progression in patients with ALS by around 2-3 months.

#### **Motor neuron disease: management**



Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

#### Riluzole

- prevents stimulation of glutamate receptors
- used mainly in amyotrophic lateral sclerosis
- prolongs life by about 3 months

#### Respiratory care

- non-invasive ventilation (usually BIPAP) is used at night
- studies have shown a survival benefit of around 7 months

#### Prognosis

- poor: 50% of patients die within 3 years

#### Question 6 of 295

A 60-year-old male presents to his neurology follow-up clinic after being diagnosed with motor neurone disease 6 months ago. Unfortunately, he reports increasing immobility since his diagnosis. While he was working full-time as a lawyer 6 months ago, he is now mostly bedbound and his wife has become his full-time carer. He was initially started on riluzole but this was stopped 2 months ago after his blood tests revealed a liver transaminitis, likely secondary to riluzole. He is seeing you in clinic for an alternative treatment but is only interested in therapeutics that will prolong his life. What is the most appropriate next step in management?

[Intravenous immunoglobulins6%Oral prednisolone4%Respiratory physiotherapy8%Non-invasive ventilation76%Pneumococcal and influenza vaccinations6%](#)

Unfortunately, riluzole is the only drug that has been proven to demonstrate a disease modifying effect in motor neurone disease, increasing survival from diagnosis from 12 to 15 months<sup>1</sup>. Although genetic studies have implicated superoxide dismutase-1 (SOD1) as a pathogenic mechanism for MND, other therapies to reduce oxidative stress have so far been unsuccessful, such as the addition of vitamin E and N-acetylcysteine (NAC). Non-invasive ventilation is the only other therapy that seems to prolong life expectancy but only if the patient can tolerate

greater than 4 hours of NIV per day and without severe bulbar dysfunction<sup>2</sup>. As a result, NIV is recommended by NICE<sup>3</sup> and the American Academy of Neurology<sup>2</sup> when the patient has developed signs of respiratory distress, type 2 respiratory failure, forced vital capacity has decreased below 50% or the patient has reported orthopnoea. However, patients with severe bulbar palsy or cognitive impairment are excluded.

1. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;3:CD001447
2. Miller RG, Jackson CE, Kasarskis EJ et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology; 2009;73(15):1218
3. NICE CG 105. Motor neurone disease- non-invasive ventilation. July 2010

## **Motor neuron disease: management**

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

### **Riluzole**

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### **Respiratory care**

- non-invasive ventilation (usually BIPAP) is used at night
- studies have shown a survival benefit of around 7 months

### **Prognosis**

- poor: 50% of patients die within 3 years

### Question 7 of 295

You have been referred a 45-year-old man by the Accident and Emergency doctors with a severe headache. The headache woke him up at 3am, and he describes it as the worst headache he's ever had. He has had two episodes like this over the past three days that have followed a very similar pattern, each lasting around 70 minutes before going. The pain is mainly around the left eye and temple and is sharp in nature. On examining him you note that his left eye is watering and swollen, and there's some redness and mild bruising just above the eye. When you ask him about this bruising he says that the pain was so bad he banged his head against the fridge door to try and help take it away.

How would you treat his headache?

[Oral triptan5%](#)[Indometacin8%](#)[100% oxygen and indometacin15%](#)[100% oxygen19%](#)[100% oxygen and nasal triptan54%](#)

What is described above is the classical cluster headache. NICE guidelines characterise cluster headaches as one-sided headache in or around the eye or temporal region associated with signs of autonomic dysfunction on the same side.

Attacks of pain:

- Usually last for 15-180 minutes
- Almost always described as the most severe pain known
- Tend to recur at the same time each day
- Often wake the person shortly after falling asleep

Signs of symptoms of autonomic dysfunction include:

- Rhinorrhoea or nasal congestion
- Red eye and/or lacrimation
- Facial or forehead sweating or flushing
- Constriction of the pupil and/or ptosis
- Eyelid oedema
- A sense of aural fullness

The suggested first line treatment for cluster headaches is 100% oxygen at a flow rate of at least 12 litres per minute and a subcutaneous or nasal triptan. Evidence from one small study suggests that subcutaneous sumatriptan provides faster relief of symptoms than intranasal sumatriptan.

Indometacin is used in paroxysmal hemicrania which has similar characteristics to cluster headaches, but attacks tend to be shorter (2-45 minutes) and more frequent (up to 40/day) and more common in women.

Oral triptans have no evidence base in cluster headaches.

<http://cks.nice.org.uk/headache-cluster> - guidelines on cluster headache investigation and management

<http://cks.nice.org.uk/headache-assessment#!scenario recommendation:4> - diagnosis

## **Cluster headache**

Cluster headaches are known to be one of the most painful conditions that patients can have the misfortune to suffer. The name relates to the pattern of the headaches - they typically occur in clusters lasting several weeks, with the clusters themselves typically once a year.

Cluster headaches are more common in men (3:1) and smokers. Alcohol may trigger an attack and there also appears to be a relation to nocturnal sleep.

### **Features**

- pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- clusters typically last 4-12 weeks
- intense sharp, stabbing pain around one eye (recurrent attacks 'always' affect same side)
- patient is restless and agitated during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

### **Management**

- acute: 100% oxygen (80% response rate within 15 minutes), subcutaneous triptan (75% response rate within 15 minutes)
- prophylaxis: verapamil is the drug of choice. There is also some evidence to support a tapering dose of prednisolone
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

Some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

### Question 8 of 295

A 76-year-old gentleman with diabetes mellitus was referred to a specialist memory clinic by his family doctor. His wife was concerned as he had been more forgetful recently and had developed urinary incontinence. His family doctor had treated him with a course of trimethoprim for a urinary tract infection but his symptoms had persisted.

On examination this gentleman smelt strongly of urine. He had a broad-based, unsteady gait. Examination of his cardiovascular and respiratory systems was unremarkable but on abdominal examination there was suprapubic tenderness. He was orientated to place but scored only 22/30 on a Mini Mental State Examination (MMSE).

#### Urinalysis:

Blood -  
Protein Trace  
Nitrites -  
White cells +  
Microscopy 50 white cells seen, bacteria +  
Cultures Mixed growth, please send repeat sample

Magnetic Resonance Imaging (MRI) of the brain: 'Disproportionately enlarged ventricular system compared with the degree of sulcal atrophy.'

#### Lumbar Puncture (LP):

Opening pressure	18 cmH <sub>2</sub> O (12 20)
Appearance	Clear and colourless
Red cells	4
White cells	1 (0 5)
Gram stain	No organisms seen
Culture	No organisms seen
Protein	30 mg/100ml (15 60)
Glucose	98mg/100ml (50 80)
Virology	No viruses detected on PCR
Cytology	No abnormal cells seen
Timed 10 metre walk pre-LP	15 seconds
Timed 10 metre walk post-40 mL CSF drainage	12 seconds

Given the underlying diagnosis what is the definitive treatment of choice?

[Repeated therapeutic lumbar punctures9% Acetazolamide12% Referral for a ventriculo-peritoneal shunt 68% Vitamin B12 and folate replacement5% Referral for lumbar drain insertion5%](#)

This gentleman presents with all three components of the classic triad of Normal Pressure Hydrocephalus (NPH): urinary incontinence, ataxia and memory impairment. He may also have a co-existent urinary tract infection but this alone cannot explain his presentation. Further evidence to support a diagnosis of NPH includes the MRI scan, which shows ventricular enlargement, and the improvement in his 10 metre walk time following therapeutic CSF drainage.

This gentleman needs a referral to the neurosurgical team for consideration of a definitive surgical procedure. There are alternative surgical options and the specifics of each particular case will dictate which approach is used. The most commonly performed procedure is ventriculo-peritoneal shunting as this has a lower failure rate than alternative procedures.

Repeated therapeutic lumbar punctures (LP) can be performed but this approach has fallen out of favour as it is unpopular with patients and exposes them repeatedly to an invasive procedure with associated risks.

Acetazolamide is a diuretic used to treat Idiopathic Intracranial Hypertension and does not have a role in NPH.

Vitamin B12 and folate replacement is not indicated in this case although vitamin B12 deficiency can cause memory impairment and walking problems (subacute combined degeneration of the cord).

A lumbar drains diverts CSF from the lumbar subarchnoid space to the outside world. It can be useful in determining whether or not a patient may respond well to a shunting procedure but due to the high risk of infection it is not in itself a definitive treatment for NPH.

## **Normal pressure hydrocephalus**

Normal pressure hydrocephalus is a reversible cause of dementia seen in elderly patients. It is thought to be secondary to reduced CSF absorption at the arachnoid villi. These changes may be secondary to head injury, subarachnoid haemorrhage or meningitis.

A classical triad of features is seen

- urinary incontinence
- dementia and bradyphrenia
- gait abnormality (may be similar to Parkinson's disease)

It is thought around 60% of patients will have all 3 features at the time of diagnosis. Symptoms typically develop over a few months.

### Imaging

- hydrocephalus with an enlarged fourth ventricle
- in addition to the ventriculomegaly there is typically an absence of substantial sulcal atrophy

### Management

- ventriculoperitoneal shunting
- around 10% of patients who have shunts experience significant complications such as seizures, infection and intracerebral haemorrhages

### Question 9 of 295

A 59-year-old male presents with 4-day history of sudden onset visual disturbance in his right eye. He reports it to be his first episode with no previous history of visual problems. His past medical history includes type 2 diabetes mellitus, hypertension and raised BMI. He is an active smoker of 40 pack years.

On examination, a right relative afferent papillary defect is detected. Pupils were equal in size. A visual field defect is demonstrated in the inferior nasal field of the right eye without a precise quadrantanopia or altitudinal pattern. Temporal arteries are non-tender and not thickened. Visual acuity on Snellen chart in left eye was 6/6, 6/18 in right. Colour vision on Ishihara plates were 17/17 on left, 5/17 on right. Fundoscopy is unremarkable. Examination of the upper and lower limbs are unremarkable, no language deficits are noted. Auscultation revealed normal heart sounds and no bruits.

His blood tests are as follows:

Hb	154 g/l
Platelets	$190 \times 10^9/l$
WBC	$7.8 \times 10^9/l$
ESR	5 mm/hr

Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	3.9 mmol/l

Urea 5.6 mmol/l  
Creatinine 80 µmol/l

What is the most likely diagnosis?

[Right retinal infarct 20%](#)[Right temporal arteritis 7%](#)[Right non-arteritic ischaemic optic neuropathy 52%](#)[Left middle cerebral artery ischaemic stroke 7%](#)[Left occipital ischaemic stroke 15%](#)

Visual field defects are a common presentation in clinical practice and MRCP part 2. The first feature to notice here is the monocular presentation, which indicates the lesion must be anterior to the optic chiasm. Next, fundoscopy is unremarkable, which would be unusual for a retinal infarct, most likely secondary to central or branch retinal artery occlusion.

Typically, an acute retinal infarct should reveal a classic cherry red spot, pale fundus and possible visualisation of the embolus. On locating the lesion to be at the optic nerve, the cause must be established: typically is this optic neuritis, arteritic or non-arteritic anterior ischaemic optic neuropathy. Optic neuropathy typically produces a correlated deficit in visual acuity with colour vision, allowing differentiation from optic neuritis, where colour vision is frequently better preserved.

Lastly, this patient has a normal ESR, is under 60 and has no local or systemic features of vasculitis, particularly temporal arteritis. In addition, he has multiple vascular risk factors, making a non-arteritic ischaemic anterior optic neuropathy most likely. Management involves optimisation of vascular risk factors and there is limited evidence for a tapering dose of oral prednisolone. Most patients can expect to improve by 3 lines of a Snellen chart by 6 months.

## **Sudden painless loss of vision**

The most common causes of a sudden painless loss of vision are as follows:

- ischaemic optic neuropathy (e.g. temporal arteritis or atherosclerosis)
- occlusion of central retinal vein
- occlusion of central retinal artery
- vitreous haemorrhage
- retinal detachment

Ischaemic optic neuropathy



- may be due to arteritis (e.g. temporal arteritis) or atherosclerosis (e.g. hypertensive, diabetic older patient)
- due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve
- altitudinal field defects are seen

#### Central retinal vein occlusion

- incidence increases with age, more common than arterial occlusion
- causes: glaucoma, polycythaemia, hypertension
- severe retinal haemorrhages are usually seen on fundoscopy

#### Central retinal artery occlusion

- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina

#### Vitreous haemorrhage

- causes: diabetes, bleeding disorders
- features may include sudden visual loss, dark spots

#### Retinal detachment

- features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

#### **Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage**

<b>Posterior vitreous detachment</b>	<b>Retinal detachment</b>	<b>Vitreous haemorrhage</b>
Flashes of light (photopsia) - in the peripheral field of vision	Dense shadow that starts peripherally progresses towards the central vision	Large bleeds cause sudden visual loss
Floaters, often on the temporal side of the central vision	A veil or curtain over the field of vision	Moderate bleeds may be described as numerous dark spots
	Straight lines appear curved	Small bleeds may cause floaters
	Central visual loss	

### Question 10 of 295

A 36-year-old lady on natalizumab for relapsing-remitting multiple sclerosis develops left leg weakness. Over 3 weeks this progresses to left hemiparesis and visual impairment. She also notices poor memory and struggles to process numbers at work as an accountant. Examination reveals left-sided 4/5 power, right homonymous hemianopia, and an abbreviated mini-mental state score of 21/30. Routine blood tests are unremarkable. MRI brain shows new multiple confluent lesions in the parietooccipital and right motor white matter areas as well as the left occipital area, with no mass effect or enhancement. Which of the following tests is likely to be most helpful in establishing a diagnosis?

[Serum glucose](#)4%[HIV serology](#)7%[JC Virus serology](#)76%[Cerebral angiogram](#)8%[Full blood count \(FBC\)](#)5%

The diagnosis here is progressive multifocal leukoencephalopathy (PML). This is a demyelinating disease of the CNS characterised by widespread lesions due to brain infection of oligodendrocytes by the JC Virus (JCV). These are visible on an MRI and have a characteristic appearance. The signs correspond to the areas occupied by the lesions. PML occurs almost exclusively in immunocompromised patients such as those with HIV or on immunotherapy. You should consider PML in your differential in such patients when they present with new odd neurology and an abnormal MRI scan.

This question's other aim is to introduce to you one of the newer therapies in multiple sclerosis (MS) called natalizumab. It is actually very frequently used in MS and indeed now approved for the treatment of relapsing-remitting MS (RRMS) in more than 50 countries. It is a monoclonal antibody that inhibits the migration of leucocytes into the central nervous system, hence reducing inflammation and demyelination. It is given as an IV infusion once a month. It is indicated in patients getting relapses despite treatment with interferon-beta or patients who just have rapidly evolving severe RRMS. It has been shown to decrease the risk of progression of disability by 42-54% and the annualised rate of relapse by 68%. The two principle side-effects are hepatotoxicity and increased PML risk, and we monitor patients for these with monthly liver function tests (LFTs) and 6-monthly JCV serology. It would not be unreasonable of them to expect you to know something about natalizumab in the exam (especially to recognise PML as a side-effect) given that the drug is now in such common use.

### Multiple sclerosis: management

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

## **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

## **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

## **Some specific problems**

### **Fatigue**

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

### **Spasticity**

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

### **Bladder dysfunction**

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying
  - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line

#### Question 1 of 285

A 25-year-old woman presents to the neurology outpatient clinic with a month history of worsening headache.

The headache is mostly frontal in nature but does move to the back of her head sometimes. It never goes away but is worst in the morning. It is throbbing in nature. In the last week it has begun to make her feel sick, although she has not vomited. She has also developed a thudding sound in her ears which she first noticed when trying to go to sleep at night but now sometimes hears at other times. She has no change in her vision or photophobia.

She has no past medical history of note and has no allergies. Her only current medication is the oral contraceptive pill. She is obese, drinks no alcohol and smokes ten cigarettes per day.

On examination her heart rate is 90/min and her blood pressure is 165/94 mmHg. Her pupils are equal and reactive and her visual fields are full to confrontation. Vision is 6/6 in both eyes and extra-ocular movements are normal. Fundoscopy reveals slight blurring of the optic disc margins with a normal retina.

Examination of the other cranial nerves reveals no deficits. On examination of the upper and lower limbs, tone, power, coordination and reflexes are all normal, with downgoing planters. Her BMI is 31.

Blood tests:

Hb 150 g/l

Platelets  $250 \times 10^9/l$

WBC  $7 \times 10^9/l$

Na<sup>+</sup> 136 mmol/l

K<sup>+</sup> 4 mmol/l

Urea 6 mmol/l

Creatinine 72  $\mu$ mol/l

What is the next most appropriate imaging investigation?

[CT angiogram head](#)8%[CT head without contrast](#)20%[MR angiogram head](#)11%[MRI head without contrast](#)11%[MR venogram head](#)50%

This lady has headache, worse on laying down, associated with nausea, pulsating tinnitus and papilloedema. These symptoms are suggestive of raised intracranial pressure and idiopathic intracranial hypertension. She is high risk for this condition given her young age, obesity and use of the oral contraceptive pill.

The diagnosis is supported by her lack of localising neurology. She does not yet have signs of visual impairment.

Formal diagnosis (by Modified Dandy criteria), requires CSF opening pressure greater than 25 cmH<sub>2</sub>O and normal brain imaging. Imaging is required to exclude venous sinus thrombosis, which could result in the same signs and symptoms and is also more common in women on the oral contraceptive pill. The gold standard imaging for this would be MRI with contrast of the head and orbits and MR venogram.

References:

Blouse V, Bruce BB, Newaman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 2012;83:488-494.

Higgins JN et al. MR venography in idiopathic intracranial hypertension: unappreciated and misunderstood. J Neurol Neurosurg Psychiatry. 2004;75(4):621-5.

## **Idiopathic intracranial hypertension**

Idiopathic intracranial hypertension (also known as pseudotumour cerebri and formerly benign intracranial hypertension) is a condition classically seen in young, overweight females.

Features

- headache
- blurred vision
- papilloedema (usually present)
- enlarged blind spot
- sixth nerve palsy may be present

## Risk factors

- obesity
- female sex
- pregnancy
- drugs\*: oral contraceptive pill, steroids, tetracycline, vitamin A, lithium

## Management

- weight loss
- diuretics e.g. acetazolamide
- topiramate is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

\*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

## Question 2 of 285

A 55 year old man presents to the Accident and Emergency department and a medical referral is requested. He reports that for the past week he has been hearing voices. He states that he cannot recognise who the voices are as they are whispering quietly but he thinks that they are making derogatory comments about him. He denies any visual hallucinations and you cannot illicit any delusional beliefs. His mood appears euthymic.

He tells you that he has a long history of alcohol dependence lasting for 30 years drinking approximately 10 units of alcohol a day on average. He tells you that in the past he has tried to stop drinking alcohol but this has caused admission to hospital due to seizures. He is particularly worried because he has cut down on alcohol since the hallucinations because he is worried that he is going mad. He is now only drinking 2 units a day and has not drunk any alcohol for 24 hours. On one previous occasion where he abstained from alcohol he said that he had hallucinations and had to be admitted to hospital for a few days and put on a drip and was told that he almost died.

Na<sup>+</sup> 144 mmol/l  
K<sup>+</sup> 3.6 mmol/l  
Urea 14.1 mmol/l  
Creatinine 119 µmol/l

Bilirubin 36 µmol/l  
ALP 199 u/l  
ALT 92 u/l  
γGT 271 u/l  
Albumin 36 g/l

He has a family history of alcohol dependence and depression but no other psychiatric problems. His medications include Omeprazole, Vitamin B, Thiamine and Diazepam.

On examination his GCS is 15, there is no tremor or sweating Pulse 80 regular BP 138 / 74 chest clear, abdo soft non tender, no peripheral focal neurology MMSE 28/30 He is commenced on chlordiazepoxide and observed for 24 hours. His GCS remains at 15 and his repeat physical examination remains unchanged and the hallucinations are still present

What is the most likely diagnosis?

[Late onset schizophrenia 17% Delirium tremens 15% Alcohol withdrawal syndrome 13% Alcoholic hallucinosis 48% Hepatic encephalopathy grade 27%](#)

Alcoholic hallucinosis is a rare condition that can occur during intoxication or withdrawal, but occurs without a clouding of consciousness. Characteristically there are auditory hallucinations which can be vague at first but then can develop into clear voices with a derogatory or persecutory content. The hallucinations normally resolve after less than 6 months.

Delirium tremens will present with a clouding of consciousness and a fluctuating or reduced GCS should be seen when the patient is observed. Also in Delirium Tremens, visual hallucinations are more common, with Lilliputian hallucinations being characteristic of this condition.

Alcohol withdrawal syndrome does not typically cause auditory hallucinations. In addition there is no evidence of a withdrawal syndrome as his pulse is normal there is no sweating or tremulousness. It is possible he has been self medicating with diazepam during his period of abstinence from alcohol.

Schizophrenia is unlikely as a diagnosis as the symptoms are too acute. In addition, affective changes and delusions and family and personal history would be more likely with a diagnosis of schizophrenia.

Hepatic encephalopathy is not the diagnosis. Although there are deranged LFTS, there is no reduction in GCS and there is no liver flap. In grade 2 encephalopathy there should be definite impairment of concentration and attention. However, this is not seen in this individual as evidenced by the high score on the MMSE

## **Alcoholic hallucinosis**

Alcoholic hallucinosis is a psychiatric disorder considered separate from alcohol withdrawal, Wernicke's/Korsakoff's

Defined as

- a psychosis of less than 6 months duration
- auditory hallucinations, often of persecutory or derogatory nature
- occurs in clear consciousness

### Question 3 of 285

An 82-year-old man is referred to neurology clinic with slowness. He presented with his wife who reported that he has been becoming progressively slower in his movements and his facial expressions have become more limited. His symptoms have progressed rapidly following the onset of dizziness a few weeks ago. He has a past medical history of type two diabetes, hypertension, high cholesterol, previous hemicolectomy for diverticulitis. His current medications include ramipril, atorvastatin, paracetamol, amlodipine, metformin, prochlorperazine and gliclazide.

On examination, he has a coarse bilateral tremor at rest, and rigidity in both arms. He has a slow gait as well. What is the most likely diagnosis?

[Parkinson's disease11%](#) [Drug-induced parkinsonism56%](#) [Multi-system atrophy15%](#) [Vascular parkinsonism15%](#) [Wilson's disease4%](#)

The answer is drug-induced parkinsonism. There are several hints to why this is more likely. A bilateral tremor of rapid onset makes drug-induced parkinsonism a more probable cause when compared to Parkinson's disease. The recent dizziness suggests that prochlorperazine was only recently introduced, making it more suspicious that it may be the cause of the current symptoms.



Vascular parkinsonism would have a more step-wise progression with definitive days of significant deterioration, which are not described here. Multi-system atrophy generally has greater autonomic involvement, as well more cerebellar dysfunction. Wilson's disease typically occurs in younger patients, and is also associated with liver dysfunction.

Source:

Chou, Kelvin L. 'Back Diagnosis and Differential Diagnosis of Parkinson Disease.' Ed. Howard I. Hurtig and John F. Dashe. UpToDate. 26 May 2016.

### **Parkinson's disease: features**

Parkinson's disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.. This results in a classic triad of features: bradykinesia, tremor and rigidity. The symptoms of Parkinson's disease are characteristically asymmetrical.

#### Epidemiology

- around twice as common in men
- mean age of diagnosis is 65 years

#### Bradykinesia

- poverty of movement also seen, sometimes referred to as hypokinesia
- short, shuffling steps with reduced arm swinging
- difficulty in initiating movement

#### Tremor

- most marked at rest, 3-5 Hz
- worse when stressed or tired
- typically 'pill-rolling', i.e. in the thumb and index finger

#### Rigidity

- lead pipe
- cogwheel: due to superimposed tremor

### Other characteristic features

- mask-like facies
- flexed posture
- micrographia
- drooling of saliva
- psychiatric features: depression is the most common feature (affects about 40%); dementia, psychosis and sleep disturbances may also occur
- impaired olfaction
- REM sleep behaviour disorder

**Drug-induced parkinsonism** has slightly different features to Parkinson's disease:

- motor symptoms are generally rapid onset and bilateral
- rigidity and rest tremor are uncommon

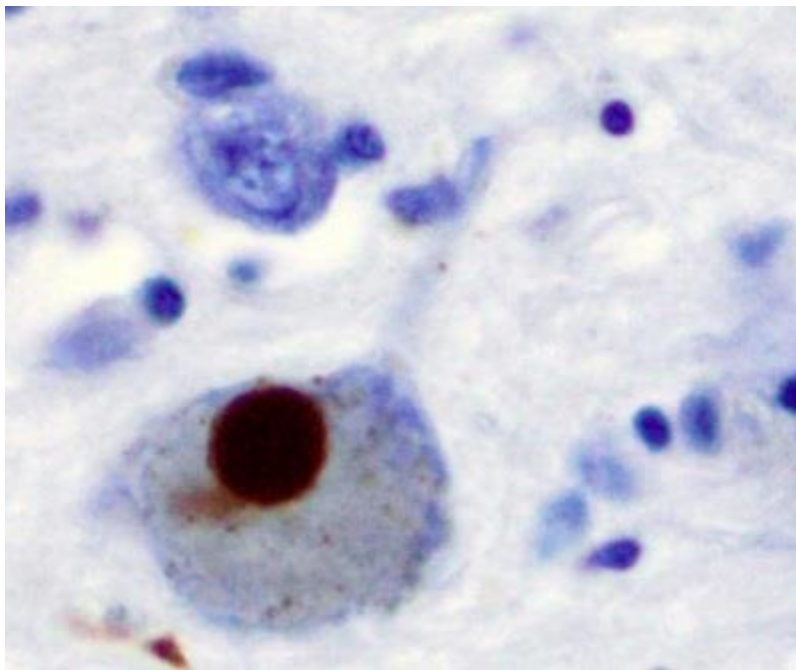


Image sourced from [Wikipedia](#)

A Lewy body (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein.

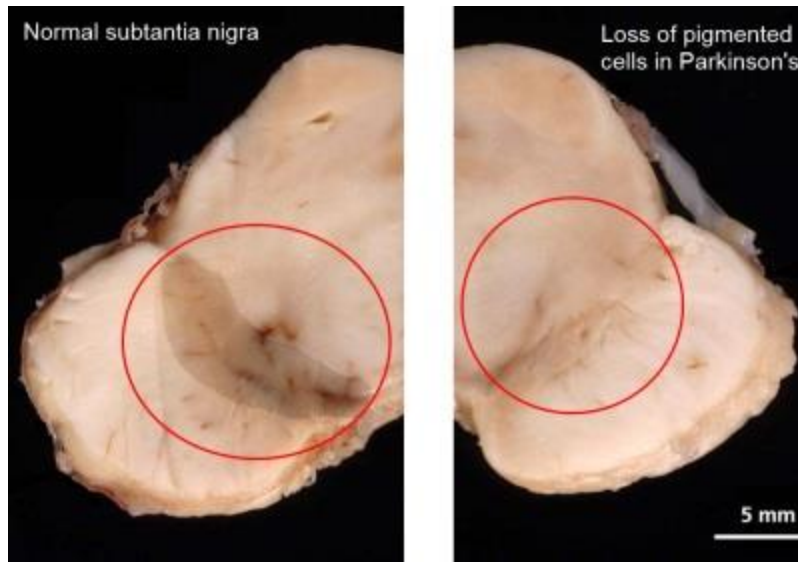


Image sourced from [Wikipedia](#)

Discoloration of the substantia nigra due to loss of pigmented nerve cells.

Question 4 of 285

A 75 year old man with Parkinson's disease is brought to see you in clinic by his son. He has become increasingly concerned that his neighbours have been watching him, and have put wiring throughout his walls to monitor his movements. He has also been describing visual hallucinations of animals climbing up his walls. His son is concerned that he has become increasingly anxious. He is currently on co-careldopa, ropinirole, and rasagiline. What is the best course of action?

[Initiate a 'drug holiday' withholding all but co-careldopa for 1 week](#)21%[Reduce ropinirole](#)43%[Reduce rasagiline](#)15%[Refer for cognitive behavioural therapy](#)6%[Start quetiapine](#)15%

This gentleman is displaying psychotic symptoms. Psychosis in Parkinson's disease (PD) can be due to the disease process itself (non-motor feature of PD), or medication side effect. It is sensible to perform a medication review and alter any potentially precipitating drugs.

Ropinirole is a dopamine agonist and is associated with psychosis, and in particular visual hallucinations. It is also important to warn all patients initiated on dopamine agonists of the potential for impulsive behaviour disorders including gambling and excessive spending.

Abrupt discontinuation of medication is never indicated in Parkinson's disease since this can lead to rapid deterioration and worsening of symptoms.

## **Parkinson's disease: management**

Currently accepted practice in the management of patients with Parkinson's disease (PD) is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, levodopa is sometimes used as an initial treatment.

### Dopamine receptor agonists

- e.g. Bromocriptine, ropinirole, cabergoline, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide\*) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
- patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence
- more likely than levodopa to cause hallucinations in older patients. Nasal congestion and postural hypotension are also seen in some patients

### Levodopa

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- unwanted effects: dyskinesia (involuntary writhing movements), 'on-off' effect, dry mouth, anorexia, palpitations, postural hypotension, psychosis, drowsiness
- no use in neuroleptic induced parkinsonism

### MAO-B (Monoamine Oxidase-B) inhibitors

- e.g. Selegiline
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

### Amantadine

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
- side-effects include ataxia, slurred speech, confusion, dizziness and livedo reticularis

## COMT (Catechol-O-Methyl Transferase) inhibitors

- e.g. Entacapone, tolcapone
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
- used in conjunction with levodopa in patients with established PD

## Antimuscarinics

- block cholinergic receptors
- now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g. procyclidine, benztropine, trihexyphenidyl (benzhexol)

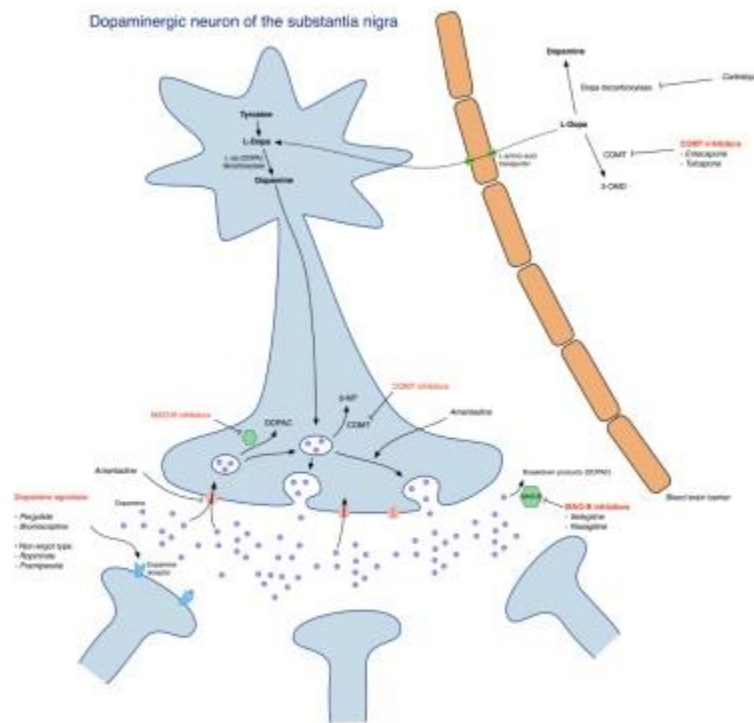


Image sourced from [Wikipedia](#)

Diagram showing the mechanism of action of Parkinson's drugs

\*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

### Question 1 of 280

A 28 year old female psychiatric nurse presents to the A+E department following a 2 minute tonic clonic generalised seizure, which self terminated. Whilst taking the history the following morning, she tells you that over the last 48 hours she has become increasingly unwell. She has been feeling increasingly anxious and has been having insomnia and vivid nightmares which wake her from sleep. She says that everything around her no longer looks real but more like a photocopy. Bowel and bladder movements have been normal. She feels generally weak and asks the lights to be dimmed in the examination room. When the nurse bell goes off in the next cubicle, she has to cover her ears.

On examination, she appears anxious, she is perspiring, respiratory rate 16/min, blood pressure 142/86 mmHg, heart rate 115 reg, sats 98% on air. You notice a fine tremor, especially in the hands and eyelids. GCS = 15. Oriented in time place and person. When you examine her, she tells you that it feels as if her legs are floating off the bed even though they are stationary. There is no flushing of the face

From looking at the computer records, you can see that she has a history of panic disorder treated with PRN lorazepam and sertraline 1 year ago. and has been treated for depression in the past. You also note from your records that she presented to A+E 5 days ago due to stress as she was sacked from her job.

Hb 13.6 g/dl  
Platelets  $232 \times 10^9/l$   
WBC  $6.9 \times 10^9/l$

Na<sup>+</sup> 142 mmol/l  
K<sup>+</sup> 3.8 mmol/l  
Urea 6.2 mmol/l  
Creatinine 81  $\mu\text{mol/l}$

What is the most likely diagnosis?

[Benzodiazepine withdrawal](#)47%[Atypical Panic attack secondary to panic disorder](#)17%[LSD intoxication](#)19%[Benzodiazepine excess](#)10%[Opiate withdrawal](#)7%

Benzodiazepine withdrawal can cause physical symptoms such as tachycardia, sweating, fine tremor which is more prominent in the tongue, eyelids and hands. It can also cause nightmares and insomnia, anxiety and phobic symptoms as well as seizures, hypersensitivity to light, sounds and touch. They can also experience derealisation (an unpleasant subjective experience that the outside world does not look real to them) and kinaesthetic hallucinations. Other symptoms

include malaise and tinnitus and it sometimes can present as a delirium.

Some factors in the history also point towards this as being a likely diagnosis. She has a history of panic disorder and previous prescription for benzodiazepines when she may have developed dependence. As a psychiatric nurse, she may have access to benzodiazepines off prescription. The fact that she has recently lost her job may mean that she has ran out of her supply and is now suffering from withdrawal syndrome.

An overdose of benzodiazepines would not present with tachycardia, sweating and anxiety. LSD intoxication could present with hallucinations, anxiety, tachycardia and sweating, however the duration of symptoms is too long for LSD unless multiple doses were taken and LSD intoxication. LSD is not linked to causing seizures. This presentation has many features of a panic attack but would not explain the seizure or kinaesthetic hallucination.

Opiate withdrawal could present in a similar way, however, you would expect to see a marked degree of GI disturbance in this syndrome and is not linked with kinaesthetic hallucinations or derealisation. In this question, the history of previous benzodiazepine usage makes this answer less likely

## **Benzodiazepines**

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by increasing the **frequency** of chloride channels. They therefore are used for a variety of purposes:

- sedation
- hypnotic
- anxiolytic
- anticonvulsant
- muscle relaxant

Patients commonly develop a tolerance and dependence to benzodiazepines and care should therefore be exercised on prescribing these drugs. The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine. The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight. A suggested protocol for patients experiencing difficulty is given:

- switch patients to the equivalent dose of diazepam

- reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
- time needed for withdrawal can vary from 4 weeks to a year or more

If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome. This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- insomnia
- irritability
- anxiety
- tremor
- loss of appetite
- tinnitus
- perspiration
- perceptual disturbances
- seizures

#### GABA<sub>A</sub> drugs

- benzodiazepines increase the **frequency** of chloride channels
- barbiturates increase the **duration** of chloride channel opening

#### Frequently Bend - During Barbeque

...or...

Barbiturates increase **duration** & Benzodiazepines increase **frequency**

#### Question 2 of 280

A 34 year old man attended the Emergency Department after experiencing a severe sudden onset headache at home. The pain was felt across the whole of the head and reached a 10/10 severity within a few seconds of onset. Since the headache began the patient had experienced a loud pulsatile pounding noise in his right ear. There was no reported loss of consciousness or other neurological symptoms. In the preceding days the patient had been fit and well. On close questioning he recalled that that morning he had been struck hard in the face by a soccer ball while watching his son's team.



The patient had no significant past medical history and took no medications. There was no family history of neurological disease.

On examination, the patient's right pupil was constricted compared to his left, with both pupils reactive to light. There was a partial ptosis of the right eye. Cranial nerve examination was otherwise unremarkable except for possible right hypoglossal palsy. Examination of the remainder of the peripheral nervous system was remarkable.

Details of initial investigations are given below.

CT brain (non-contrast): no acute intracranial pathology identified; normal ventricular system; no bony injury.

Lumbar puncture:

CSF red cells 2 / mm<sup>3</sup>

CSF white cells 4 / mm<sup>3</sup>

CSF gram stain unremarkable

CSF glucose 60 % serum level

CSF protein 0.65 g / L

CSF negative for haemoglobin break down products

What is the correct diagnosis?

[Vertebral artery dissection 24%](#)[Internal carotid artery dissection 40%](#)[Posterior reversible encephalopathy syndrome 6%](#)[Reversible cerebrovascular vasoconstriction syndrome 14%](#)[Posterior communicating artery aneurysm 16%](#)

Internal carotid artery dissection can present with thunderclap headache, commonly following minor trauma, as in this case. Possible associated symptoms and signs include homolateral Horner's syndrome, tinnitus or tongue palsy. CT brain and lumbar puncture are usually normal (or near normal in the case of LP) with diagnosis confirmed by angiography.

The remaining options are all possible causes of thunderclap headache. Vertebral artery dissection would typically cause a posterior circulation stroke pattern of signs and symptoms. Reversible cerebrovascular vasoconstriction syndrome is associated with hypertension and seizures and diagnosed by arterial beeding on angiography. Posterior reversible encephalopathy syndrome is also associated with hypertension and specific changes on MRI brain secondary to vasogenic brain oedema. Posterior communicating artery aneurysm causes compression of the third nerve with unilateral mydriasis without other signs of third nerve palsy.

Ducros A, Boussier M. Thunderclap headache. BMJ 2012;345:e8557

## Thunderclap headache

Thunderclap headache describes a sudden (reaches maximum severity within seconds to minutes of onset) and severe headache.

### Causes

- subarachnoid hemorrhage
- cerebral venous sinus thrombosis
- internal carotid artery dissection
- pituitary apoplexy
- reversible cerebral vasoconstriction syndrome
- primary sexual headache
- posterior reversible leucoencephalopathy syndrome

### Question 4 of 280

As the medical registrar on-call you are fast-bleeped to see a patient in the resuscitation room of the Emergency Department.

A 27 year-old lady presented with severe breathing difficulties and hypoxia, and had become increasingly drowsy whilst in the department. Arterial blood gases performed by the emergency physicians showed:

pH 7.142  
pCO<sub>2</sub> 12.5 kPa  
pO<sub>2</sub> 9.19 kPa  
HCO<sub>3</sub> 25.3 mmol/l

Due to the rapidity of her decline, the emergency physicians tell you that only a very brief history was possible before she required intubation. She described a productive cough over the last few days, and mentioned that she was taking tablets for a neurological condition.

On examination, she is intubated and maintained on sedation with propofol. You notice a well-healed midline sternotomy scar. On auscultation of the chest there are coarse crackles audible in the left mid and lower zones.

She is transferred to the Intensive Care Unit for continued mechanical ventilation and is

commenced on empirical broad-spectrum antibiotics.

Which one of the following additional interventions will most hasten her recovery?

[Botulinum anti-toxin 5%](#) [Edrophonium 10%](#) [Plasma exchange 67%](#) [3,4-diaminopyridine 7%](#) [Steroids 11%](#)

This lady has myasthenia gravis and is taking pyridostigmine tablets for symptomatic relief. She has had a thymectomy in the past.

The acute presentation is of myasthenic crisis, with dramatically deteriorating weakness progressing to respiratory failure. Crisis is typically precipitated by infection (in this case pneumonia), or non-compliance with medication.

The initial priority is ventilatory support. Falling oxygen saturations and PaO<sub>2</sub> are late indicators of ventilatory compromise. A rising PaCO<sub>2</sub> is a more sensitive marker. Although inappropriate in this case, forced vital capacity should be measured and generally if below 1.5L ventilatory support should be considered.

In considering antibiotic cover, gentamicin should be avoided as it may interfere with neuromuscular transmission. Similarly, the anaesthetists should be warned that the patient will be extremely sensitive to small doses of non-depolarising muscle relaxants such as atracurium and vecuronium, which are commonly used for rapid sequence induction in the emergency setting.

Plasmapheresis and intravenous immunoglobulin are used to provide a rapid disease-modifying effect in myasthenic crisis. In plasma exchange, circulating anti-acetylcholine receptor antibodies are removed, relieving neuromuscular blockade and improving weakness. The major side effects are worsening of sepsis, due to removal of protective antibodies, and coagulopathy due to removal of clotting factors and destruction of platelets.

Botulinum anti-toxin is a specific treatment for botulism.

Edrophonium (Tensilon) is a short-acting acetylcholinesterase inhibitor which is used in the diagnosis of myasthenia gravis.

3,4-diaminopyridine is a specific treatment for the Lambert-Eaton myasthenic syndrome.

Steroids and other immunopressive agents may be used for the treatment of myasthenia gravis but in this case plasma exchange is preferred as a rapid response is required.

## **Myasthenia gravis**

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

#### Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

#### Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

#### Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

#### Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

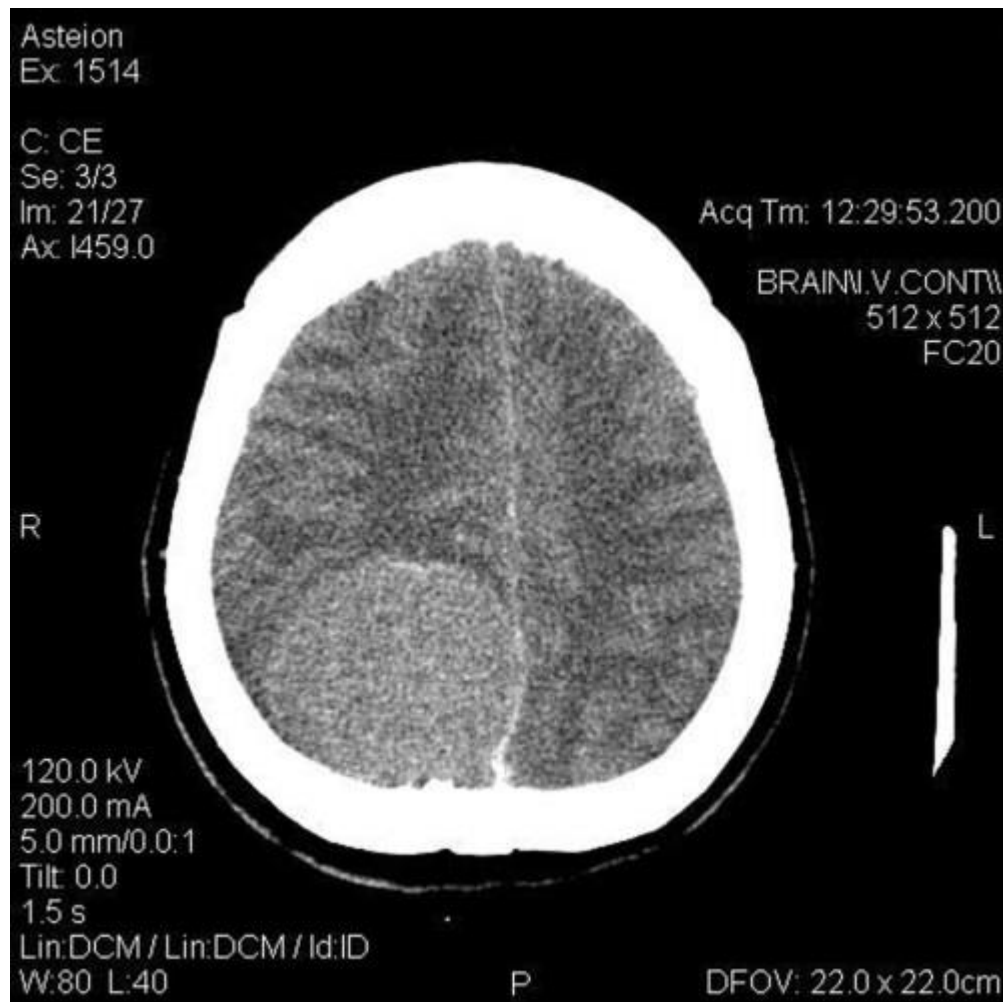
\*antibodies are less commonly seen in disease limited to the ocular muscles

Question 6 of 280

A 45-year-old woman presents to the Emergency Department due to a headache. This has been getting gradually worse over the past 3 months. Her GP has tried a number of therapies including a triptan, amitriptyline and standard analgesia with limited effect. She is a non-smoker and drinks around 30 units of alcohol per week.

Neurological examination is unremarkable.

A CT scan is arranged:



What is the most likely diagnosis?

[Extradural haematoma4%](#) [Meningioma59%](#) [Glioblastoma multiforme27%](#) [Herpes simplex encephalitis3%](#) [Subdural haematoma6%](#)

The CT shows a well defined spherical mass in the right posterior falx cerebri consistent with a meningioma. There is mild oedema and mass effect on the right lateral ventricle. The tumour is straddling the inferior surface of the falx.

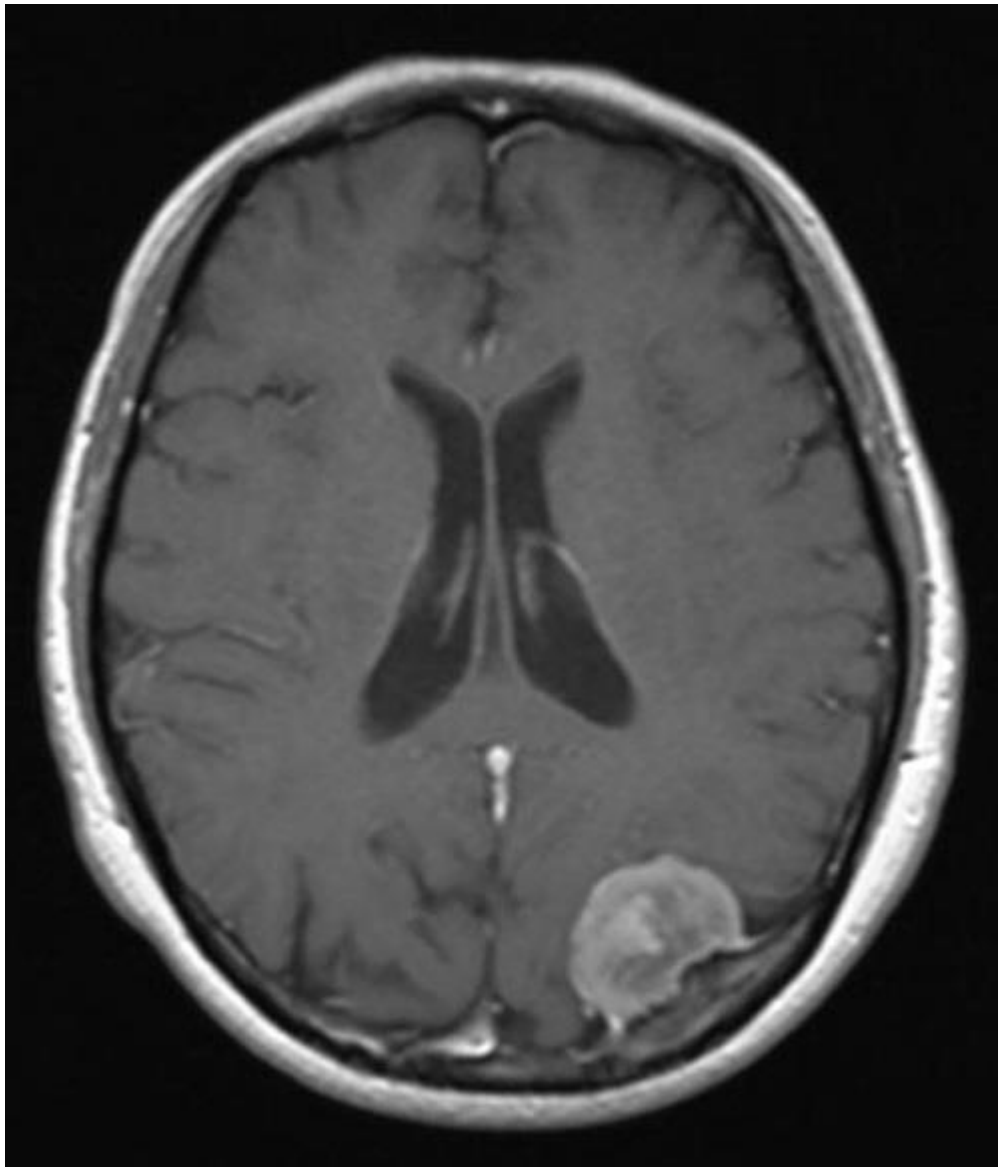
A glioblastoma multiforme would normally have a more heterogeneous appearance than shown here.

## Brain tumours

The majority of adult tumours are supratentorial, whereas the majority of childhood tumours are infratentorial.

Type of tumour	Features
Glioblastoma multiforme	<ul style="list-style-type: none"><li>• The most common primary brain tumour in adults.</li><li>• Histology: Pleomorphic tumour cells border necrotic areas</li></ul>
Meningioma	<ul style="list-style-type: none"><li>• The second most common primary brain tumour in adults</li><li>• Histology: Spindle cells in concentric whorls and calcified psammoma bodies</li></ul>
Schwannoma	<ul style="list-style-type: none"><li>• Often seen in the cerebellopontine angle: acoustic neuroma</li><li>• Bilateral schwannomas are seen in neurofibromatosis</li><li>• Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)</li></ul>
Pilocytic astrocytoma	<ul style="list-style-type: none"><li>• The most common primary brain tumour in children</li><li>• Histology: Rosenthal fibres (corkscrew eosinophilic bundle)</li></ul>
Medulloblastoma	<ul style="list-style-type: none"><li>• More common in children</li><li>• Found exclusively in the posterior fossa</li><li>• Metastases through the CSF</li><li>• Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures</li></ul>
Ependymoma	<ul style="list-style-type: none"><li>• Commonly seen in the 4th ventricle</li><li>• May cause hydrocephalus</li><li>• Histology: perivascular pseudorosettes</li></ul>
Oligodendroma	<ul style="list-style-type: none"><li>• Benign, slow-growing tumour common in the frontal lobes</li><li>• Histology: Calcifications with 'fried-egg' appearance</li></ul>

Type of tumour	Features
Haemangioblastoma	<ul style="list-style-type: none"> <li>• Vascular tumour of the cerebellum</li> <li>• Associated with von Hippel-Lindau syndrome</li> <li>• Histology: foam cells and high vascularity</li> </ul>
Pituitary adenoma	<ul style="list-style-type: none"> <li>• Most common type is a prolactinoma</li> <li>• May present with bitemporal hemianopia</li> </ul>
Craniopharyngioma	<ul style="list-style-type: none"> <li>• Most common paediatric supratentorial tumour</li> <li>• Histology: Derived from remnants of Rathke pouch</li> </ul>
Metastases	<ul style="list-style-type: none"> <li>• Most common type of brain tumour</li> </ul>



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**Meningioma** - MRI showing the typical well-circumscribed appearance. A dural tail can be where the tumour 'connects' to the dura. It is seen in around 65% of meningiomas.



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

**Glioblastoma multiforme** - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the more homogenous meningioma above.

#### Question 1 of 274

A 45-year-old lady has had weight loss over the last eight months. Over the last 3 months, she has become confused according to her family, forgetting things she would normally remember like telephone numbers or what she did during the day. She has now presented with a second episode of what sounds like a generalised tonic-clonic seizure in the last week. She has no other past medical history of note. Clinical examination shows MMSE of 23/30, cachexia, a bulky left adnexal region, and nil else. Routine blood tests are unremarkable. You organise a CT chest, abdomen, pelvis and head which reveal a suspicious lesion in the left ovary but are otherwise normal. You organise a biopsy of the left ovary, send off a paraneoplastic blood screen, and order an MRI of the brain. What would you expect the paraneoplastic screen to return showing?



Voltage-gated potassium channel antibodies7% Anti-Hu antibodies34% Anti-GAD10% Anti-Ma2 antibodies9% NMDA receptor antibodies40%

The diagnosis is limbic encephalitis. Limbic encephalitis represents a group of autoimmune conditions characterised by inflammation of the limbic system and other parts of the brain. People with limbic encephalitis typically presents with a subacute development of memory impairment, confusion, and alteration of consciousness, often accompanied by seizures and temporal lobe signal change on MRI.

It is important to diagnose the underlying autoimmune aetiology of limbic encephalitis as this might point you toward the underlying diagnosis of cancer. This is to say that limbic encephalitis may often present as a paraneoplastic syndrome, although not always. The antibodies that cause limbic encephalitis and their associated malignancies are:

NMDA receptor antibodies = ovarian cancer

Voltage-gated potassium channel antibodies = Thymoma or small cell lung cancer

Anti-Hu antibodies = Small cell lung cancer

Anti-GAD = Thymoma

anti-Ma2 antibodies = Germ-cell tumours of testis, non-small cell lung cancer

## **Autoimmune encephalitis**

Types of autoimmune encephalitis include:

- autoimmune limbic encephalitis (paraneoplastic and non-paraneoplastic)
- Rasmussen's encephalitis
- anti-NMDAR (NR1) encephalitis
- glycine-receptor mediated encephalitis
- Bickerstaff brainstem encephalitis

### **Question 3 of 274**

A 32-year-old woman presents with reduced sensation. She has noticed that slowly over six months she has not felt when hot water has splashed on her hands, despite blistering occurring afterwards. Her husband has become concerned and asked her to seek a medical opinion. She denies any other problems, including weakness, weight-loss or her activities of daily living being affected. She has a past medical history of asthma but only rarely needs her salbutamol inhaler.

She has no other medications or allergies. On examination, she has sensory loss over her hands and arms when tested for temperature and pain. There is a dermatomal distribution affecting dermatomes C4 to C6 which is symmetrical. Cranial nerve and lower limb examination is normal. Spinal examination shows no tenderness. What is the most likely diagnosis?

[Multiple sclerosis7% Cervical disc prolapse9% Vasculitis6% Myasthenia gravis4% Syringomyelia74%](#)

The correct answer is syringomyelia. The fact that she has primarily loss of spinothalamic function in a cervical nerve distribution with a distinct sensory loss makes syringomyelia the most probable diagnosis. Weakness can occur as well. Syringomyelia is caused by a tubular cyst within the central spinal cord, most commonly affecting the cervical region. It compresses corticospinal and spinothalamic tract as well as anterior horn cells. Presentation can be variable causing loss of temperature sensation, pain, paralysis, stiffness and weakness. Due to the common location of the cyst, this is most likely to affect hands, arms and shoulders. In half of the patients, there is only mild or no disability.

Multiple sclerosis is unlikely as there is no evidence of lesions separated by attacks. The absence of neck pain or tenderness makes a disc prolapse unlikely, whilst the absence of systemic features makes vasculitis unlikely. Myasthenia is associated with fatigability rather than a sensory loss.

## **Syringomyelia**

### Overview

- development of cavity (syrinx) within the spinal cord
- if extends into medulla then termed syringobulbia
- strongly associated with the Arnold-Chiari malformation

### Features

- maybe asymmetrical initially
- slowly progressives, possibly over years
- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
- loss of reflexes, bilateral upgoing plantars
- also seen: Horner's syndrome

#### Question 4 of 274

A 46-year-old Ghanaian woman was flying from Ghana to San Francisco, USA when she was noticed to be confused and behaving inappropriately on the plane. She was talking loudly to herself, complaining of a headache, and also appeared to be hearing voices. She had one episode of incontinence on the plane. During the transit in London, she was brought to the nearest hospital for investigations.

On examination, she was drowsy and slow to respond to questions. Her temperature was 37.3°C, heart rate of 98 bpm, blood pressure of 138/92 mmHg, respiratory rate of 16, and oxygen saturations were 100% on air. Her pupils were 3mm bilaterally, equal and reactive. Her neck was supple and there was mild photophobia. Her abbreviated mental test score was 6/10.

Her investigations revealed:

C Reactive protein	24 mg/l
Haemoglobin	128 g/l
White cell count	$11.6 \times 10^9/L$
HIV antibody serology	positive
HIV viral load	19000 copies/ml
CD4+ T lymphocyte count	35 cells/mm <sup>3</sup>
Na+	136 mmol/l
K+	4.9 mmol/l
Urea	7.2 mmol/l
Creatinine	108 µmol/l
Corrected calcium	2.32 mmol/l
Plasma glucose	5.8mmol/l

Chest X-Ray: Lung fields clear

Computer Tomography (CT) head scan: Hypodense lesions involving the medial temporal regions. Lesions enhance with contrast.

Cerebro-spinal fluid (CSF) analysis:

Opening pressure 20 cmH<sub>2</sub>O

Protein 1.2 g/L

White cell count 50 per mm<sup>3</sup> (predominantly mononuclear cells)

Red cell count 5 per mm<sup>3</sup>

Glucose 4.8 mmol/l

Gram stain No organisms seen

What is the next most appropriate management step?

[Intravenous acyclovir 45% Oral prednisolone 5% Highly Active Anti-Retroviral Therapy \(HAART\) 10% Intravenous fluconazole 7% Pyrimethamine and Sulfadiazine 33%](#)

This lady is immunocompromised with a new diagnosis of HIV, and has an altered conscious level, with psychotic symptoms suggestive of encephalitis. Her CT head scan shows the involvement of the medial temporal region, which is highly suggestive of herpes encephalitis, and this is supported by the LP results with raised protein levels, and a predominantly mononuclear white cell picture. Viral polymerase chain reaction (PCR) is the gold standard in the diagnosis of herpes encephalitis, and management for Herpes encephalitis is high-dose intravenous acyclovir to achieve central nervous system penetrance.

Although this lady has advanced HIV infection, there is some evidence that starting HAART may cause an immune reconstitution syndrome, resulting in an initial deterioration in the patient's condition as the immune system is boosted. Thus while she would require HAART, the initial management should be to decrease the burden of infection with acyclovir to prevent a deterioration in her condition.

There is limited evidence for steroid use in HSV encephalitis. There is no evidence of cryptococcal or toxoplasmosis infection from the CT and CSF results, which rules out options (d) and (e) respectively.

## **Herpes simplex encephalitis**

Herpes simplex (HSV) encephalitis is a common topic in the exam. The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia

### **Features**

- fever, headache, psychiatric symptoms, seizures, vomiting
- focal features e.g. aphasia
- peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis

### **Pathophysiology**

- HSV-1 responsible for 95% of cases in adults
- typically affects temporal and inferior frontal lobes

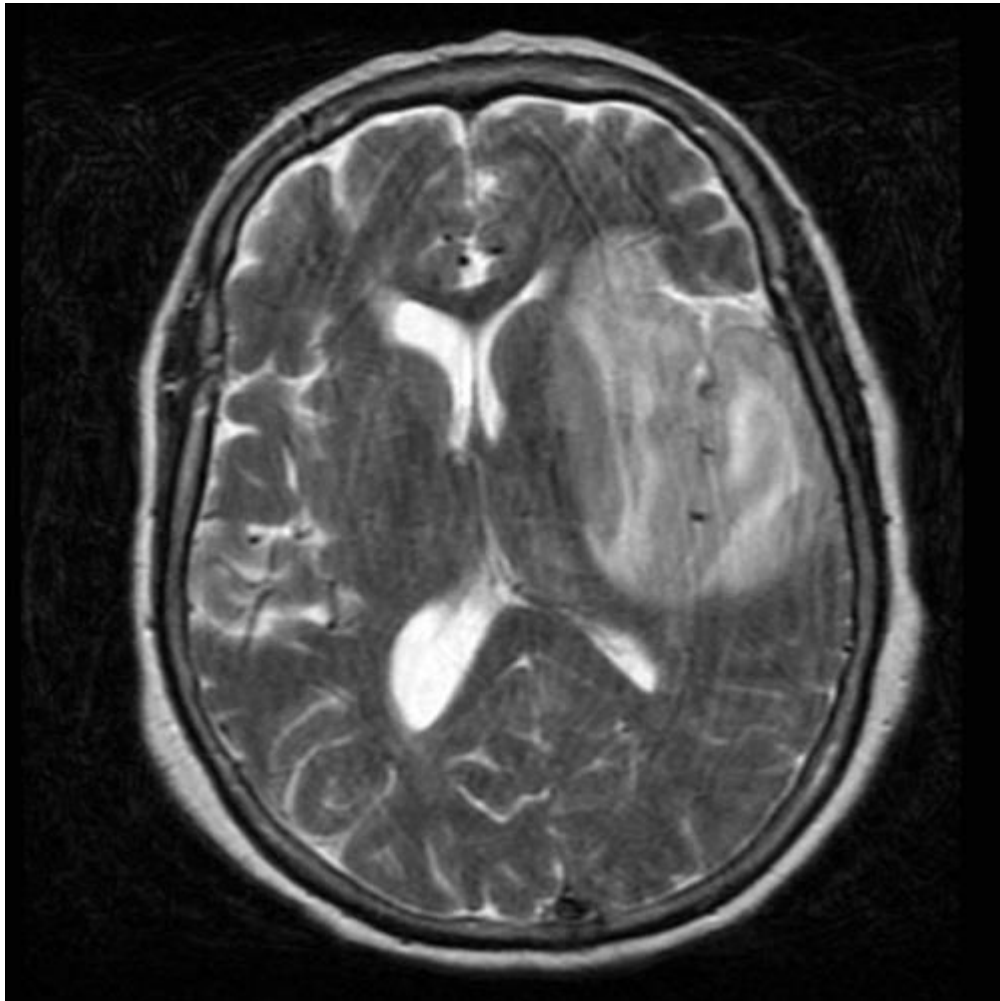
## Investigation

- CSF: lymphocytosis, elevated protein
- PCR for HSV
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) - normal in one-third of patients
- MRI is better
- EEG pattern: lateralised periodic discharges at 2 Hz

## Treatment

- intravenous aciclovir

The prognosis is dependent on whether aciclovir is commenced early. If treatment is started promptly the mortality is 10-20%. Left untreated the mortality approaches 80%





MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

#### Question 5 of 274

A 32-year-old female patient presents with 48 hours of new onset vertiginous symptoms and speech slurring. She has no past medical history and is a non-smoker. On examination, you notice a left partial ptosis and miosis. Finger-nose coordination is impaired with her left arm and she also has reduced sensation to your cold tuning fork on her left face, right arm and right leg. What is the most likely diagnosis?

[Bilateral cerebellar infarcts8%](#)[Right middle cerebral artery ischaemic infarct6%](#)[Left middle cerebral artery ischaemic infarct10%](#)[Lateral medullar brainstem infarct68%](#)[Left basal ganglia haemorrhage8%](#)

This patient describes almost all the features of lateral medullary syndrome, classically known as Wallenberg's syndrome, consisting of ipsilateral cerebellar ataxia (lesion at the inferior cerebellar peduncle), ipsilateral loss of facial pain and temperature (ipsilateral trigeminal nucleus), vertigo and nystagmus (vestibular nucleus) and Horner's syndrome (first order sympathetic chain neurones). In such a young patient without cardiovascular risk factors, vertebral artery dissection would be the most likely cause of the posterior circulation infarct, likely secondary to sudden neck twisting or extension from recent trauma, classically following a whiplash injury.

### Lateral medullary syndrome

Lateral medullary syndrome, also known as Wallenberg's syndrome, occurs following occlusion of the posterior inferior cerebellar artery

#### Cerebellar features

- ataxia
- nystagmus

#### Brainstem features

- ipsilateral: dysphagia, facial numbness, cranial nerve palsy e.g. Horner's

- contralateral: limb sensory loss

#### Question 6 of 274

A 32-year-old male presents with his 4th episode of worst ever headache in one week. He describes the headache to always be of sudden onset on the left side of his head, of 10 out of 10 severity and that he finds bright lights extremely distressing during these periods. The episodes last for around 30 minutes, typically after dinner. He also describes redness and swelling of his left eye and a blocked left nostril during the headaches, associated with tearing of his left eye.

He has no past medical history and family history of migraines. He denies illicit drug use, is a non-smoker and drinks two glasses of wine with dinner every night. Over the past 7 days, he has been self-medicating with paracetamol and ibuprofen. On examination, you notice no focal neurology, no meningism and fundoscopy is unremarkable.

What is the most likely diagnosis?

[Subarachnoid haemorrhage5%](#)[First presentations of migraine5%](#)[SUNCT \(short lasting unilateral neuralgiform headache with conjunctival injection or tearing\)27%](#)[Medication overuse headache6%](#)[Cluster headaches56%](#)

The main differentials are between cluster headaches and SUNCT, both of which are headache syndromes resulting in severely painful headaches associated with autonomic symptoms. It would be unusual for autonomic symptoms such as conjunctival injection, lacrimation and rhinorrhoea with migraines. Subarachnoid haemorrhage headaches rarely re-occur without disastrous consequences, focal neurology and reduced GCS. Medication overuse headache are normally of onset after a longer period of analgesia use and are more chronic in character without autonomic symptoms.

In distinguishing cluster headaches and SUNCT, the former are more prevalent in younger males below the age of 40 while SUNCT is more common in older patients above the age of 40. Cluster headaches typically onset at night, last from 15 minutes to 3 hours, while SUNCT can occur at any time of day and typically lasts for seconds to minutes. Cluster headaches rarely onset more than 3 times per day while SUNCT has been described in up to 75 times per day. A transient Horner's syndrome is typical during a cluster headache but may be lacking in SUNCT. Lastly, cluster headaches are classically, but not always, triggered by alcohol<sup>1</sup>. The combination of severe nocturnal onset unilateral headache following alcohol in a patient under 40 years old, lasting for 30 minutes, suggest cluster headaches over SUNCT.

1. Kruszewski P, Pareja JA, Caminero AB et al. Cluster headaches and SUNCT: similarities and differences. J Headache Pain 2001; 2:57-66

## Cluster headache

Cluster headaches are known to be one of the most painful conditions that patients can have the misfortune to suffer. The name relates to the pattern of the headaches - they typically occur in clusters lasting several weeks, with the clusters themselves typically once a year.

Cluster headaches are more common in men (3:1) and smokers. Alcohol may trigger an attack and there also appears to be a relation to nocturnal sleep.

### Features

- pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- clusters typically last 4-12 weeks
- intense sharp, stabbing pain around one eye (recurrent attacks 'always' affect same side)
- patient is restless and agitated during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

### Management

- acute: 100% oxygen (80% response rate within 15 minutes), subcutaneous triptan (75% response rate within 15 minutes)
- prophylaxis: verapamil is the drug of choice. There is also some evidence to support a tapering dose of prednisolone
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

Some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

### Question 7 of 274

A 79-year-old is brought into hospital with muscle cramps, fevers and passing dark urine. He is known to have previously had Parkinson's disease and takes Sinemet 125 five times a day. His



daughter, who normally picks up his medicine for him from the pharmacy has been called away on business for the past 5 days. As a result, the patient's supplies ran out and he has not taken his PD meds for 3 days. His blood pressure is fluctuant, from 77/52 mmHg to 150/88mm Hg. On examination, his temperature is 39.2 degrees, his heart sounds are quiet but present and chest auscultation is unremarkable. You note rigid muscles in four all limbs, no obvious superficial evidence of head injury and new confusion, with abbreviated mental test 0/10. You start intravenous fluids, intravenous broad spectrum antibiotics, catheterise the patient and insert a nasogastric tube to administer his regular medications. What is the underlying diagnosis?

[Urosepsis6%Restrictive pericarditis5%Idiopathic Parkinson's disease progression5%L-dopa dyskinesia10%Neuroleptic malignant syndrome75%](#)

The history gives a clear history of lack of access to regular Parkinsonian medications associated with pyrexia and muscle cramps. This would point towards a diagnosis of Parkinsonism-hyperpyrexia syndrome, a form of neuroleptic malignant syndrome observed when PD medications are withdrawn or changed. A key feature to be noted here is the labile blood pressure, suggesting autonomic instability, suggesting the need for careful intensive care monitoring and supportive therapy. Treatment is by replacing the original dose of withdrawn medication, either orally or via a nasogastric tube. If this is not possible intravenous L-dopa is possible while dopamine agonists can be given parenterally: rotigotine can be applied as a transdermal patch while apomorphine is available as an intravenous or subcutaneous infusion.

## **Neuroleptic malignant syndrome**

Neuroleptic malignant syndrome is a rare but dangerous condition seen in patients taking antipsychotic medication. It carries a mortality of up to 10% and can also occur with atypical antipsychotics. It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

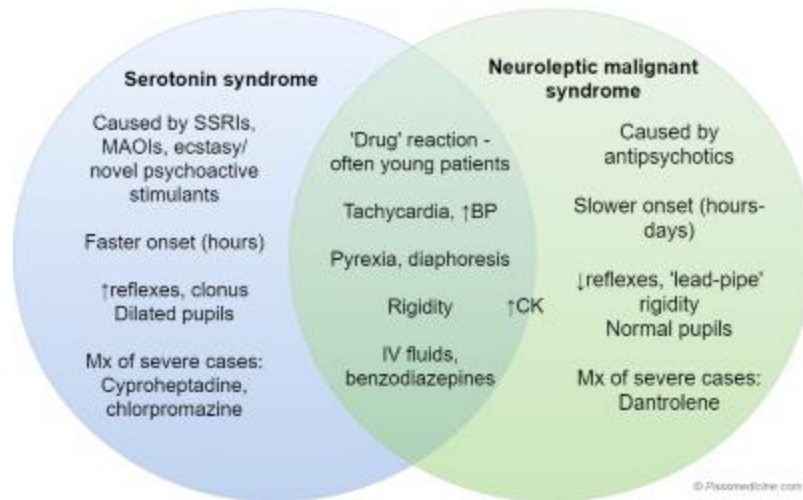
### **Features**

- more common in young male patients
- onset usually in first 10 days of treatment or after increasing dose
- pyrexia
- rigidity
- tachycardia

A raised creatine kinase is present in most cases. A leukocytosis may also be seen

### **Management**

- stop antipsychotic
- IV fluids to prevent renal failure
- dantrolene\* may be useful in selected cases
- bromocriptine, dopamine agonist, may also be used



Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

\*thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum

#### Question 8 of 274

A 28 year-old woman presents with a two month history of double vision, which is worse at the end of each day. On examination, there is bilateral ptosis which is fatiguable. There is a complex ophthalmoplegia which does not conform to the pattern of one or more cranial nerves. Examination of the limbs is unremarkable.

Which of the following would be most suggestive of a diagnosis of myasthenia gravis?

[Weakness confined to extraocular muscles6%](#) [A decremental response to repetitive nerve stimulation72%](#) [An incremental response to repetitive nerve stimulation7%](#) [Thymic enlargement seen on chest imaging10%](#) [Internuclear ophthalmoplegia5%](#)

In myasthenia gravis affected muscles show a decremental response to repetitive nerve stimulation (there is a progressive decline in the amplitude of the compound muscle action

potential with repeated stimulation).

An incremental response to repetitive nerve stimulation is seen in the Lambert-Eaton myasthenic syndrome.

Weakness confined to extraocular muscles is certainly compatible with myasthenia gravis but is not diagnostic, and may be seen in thyroid eye disease, brainstem syndromes, and mitochondrial diseases. Ocular myasthenia is the mode of presentation of around half of patients with myasthenia gravis. A proportion may go on to develop generalised disease.

Thymic hyperplasia and thymoma are commonly seen in association with myasthenia gravis, as well as other autoimmune disease. Thymectomy is indicated in all patients with thymoma, due to the risk of malignant transformation. Thymectomy in the case of thymic hyperplasia is more controversial, and is generally reserved for younger patients with generalised disease and anti-AChR antibodies.

True internuclear ophthalmoplegia occurs in lesions of the medial longitudinal fasciculus in the brainstem, and as such is not a feature of neuromuscular junction disorders such as myasthenia gravis. However, the involvement of extraocular muscles (one or both medial recti) may on occasion mimic internuclear ophthalmoplegia.

## **Myasthenia gravis**

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

### **Associations**

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

## Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

## Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

## Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

## Question 10 of 274

A 20-year-old girl with multiple sclerosis (MS) attends the emergency department following a seizure. She was diagnosed with MS at age 16 and has received different immunomodulatory regimes in the past, including azathioprine. She commenced natalizumab 2 years ago. This is her first seizure however once recovered, she tells you that she has noticed she has been increasingly clumsy over the last 6 months, she drops things easily. In addition, she has had several episodes where her speech has been slurred and people have commented that she sounds tired.

On examination, you find that her tone is normal throughout, power in all muscles groups in both upper and lower limbs is normal. On cranial nerve examination, you identify a right homonymous superior quadrantanopia however she does have a full range of eye movements and no ptosis. She has an ataxic gait. Her speech is normal throughout the history.

She is concerned, what is the diagnosis?

[Progressive multifocal leukoencephalopathy 56%](#) [Transient ischaemic attacks 7%](#) [Progression of multiple sclerosis 24%](#) [Newly diagnosed epilepsy 6%](#) [myasthenia gravis 8%](#)

Natalizumab is a humanised monoclonal antibody against the cell adhesion molecule 4-integrin and is licensed as a monotherapy for the treatment of multiple sclerosis in Europe.

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection caused by the JC virus that only occurs in patients who are immunocompromised and has a risk of 2.1 in every 1,000 using natalizumab. Patients who have taken immunosuppressants before the initiation of natalizumab therapy have the highest risk of developing PML

Bloomgren, G et al. Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. 2012 New England Journal of Medicine 366 (20): 1870-1880.

Kappos, L; Bates, D; Edan, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. 2010 Lancet neurology 10 (8): 745-758.

## **Multiple sclerosis: management**

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

### **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

### **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

## Some specific problems

### Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

### Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

### Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

### Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line

## Question 1 of 264

A 34 year-old man presents with insidious onset right hand weakness over the last week. He is right hand dominant and struggling to perform basic tasks such as opening a door with a key.

On examination he has marked weakness of thumb flexion at the interphalangeal joint and weakness of flexion of the index and middle finger. There is no detectable sensory deficit.

What is the likely diagnosis?

[C8 nerve root radiculopathy](#) 15% [Motor neurone disease](#) 6% [Median nerve palsy](#) 32% [Carpal tunnel syndrome](#) 9% [Anterior interosseous syndrome](#) 37%

Given the specific nature of the deficit described and the lack of sensory symptoms the most likely diagnosis is anterior interosseous syndrome. The anterior interosseous nerve is a pure motor branch of the median nerve. The anterior interosseous nerve supplies flexor pollicis longus and the lateral half of flexor digitorum profundus. Symptoms usually develop due to nerve compression or transient inflammation.

## Median nerve

The median nerve is formed by the union of a lateral and medial root respectively from the lateral (C5,6,7) and medial (C8 and T1) cords of the brachial plexus; the medial root passes anterior to the third part of the axillary artery. The nerve descends lateral to the brachial artery, crosses to its medial side (usually passing anterior to the artery). It passes deep to the bicipital aponeurosis and the median cubital vein at the elbow.

It passes between the two heads of the pronator teres muscle, and runs on the deep surface of flexor digitorum superficialis (within its fascial sheath).

Near the wrist it becomes superficial between the tendons of flexor digitorum superficialis and flexor carpi radialis, deep to palmaris longus tendon. It passes deep to the flexor retinaculum to enter the palm, but lies anterior to the long flexor tendons within the carpal tunnel.

## Branches

Region	Branch
Upper arm	No branches, although the nerve commonly communicates with the musculocutaneous nerve
Forearm	Pronator teres Flexor carpi radialis Palmaris longus Flexor digitorum superficialis

Region	Branch
	Flexor pollicis longus Flexor digitorum profundus (only the radial half)
Distal forearm	Palmar cutaneous branch
	Motor supply (LOAF)
Hand (Motor)	<ul style="list-style-type: none"> <li>• Lateral 2 lumbricals</li> <li>• Opponens pollicis</li> <li>• Abductor pollicis brevis</li> <li>• Flexor pollicis brevis</li> </ul>
Hand (Sensory)	<ul style="list-style-type: none"> <li>• Over thumb and lateral 2 ½ fingers</li> <li>• On the palmar aspect this projects proximally, on the dorsal aspect only the distal regions are innervated with the radial nerve providing the more proximal cutaneous innervation.</li> </ul>

### Patterns of damage

#### Damage at wrist

- e.g. carpal tunnel syndrome
- paralysis and wasting of thenar eminence muscles and opponens pollicis (ape hand deformity)
- sensory loss to palmar aspect of lateral (radial) 2 ½ fingers

#### Damage at elbow, as above plus:

- unable to pronate forearm
- weak wrist flexion
- ulnar deviation of wrist

#### Anterior interosseous nerve (branch of median nerve)

- leaves just below the elbow
- results in loss of pronation of forearm and weakness of long flexors of thumb and index finger

#### *Topography of the median nerve*



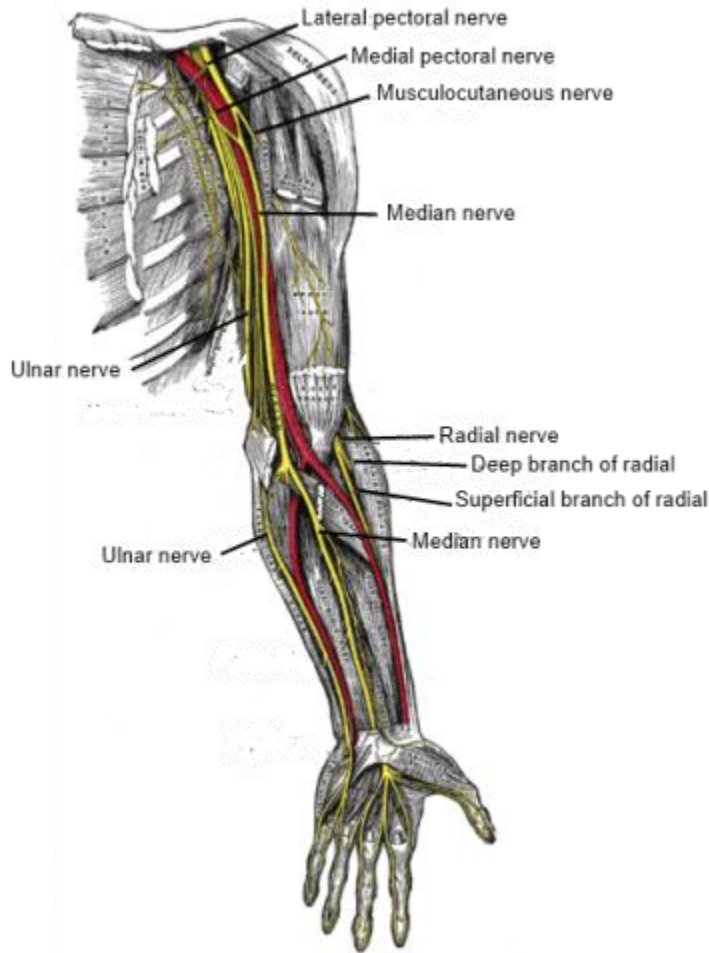


Image sourced from [Wikipedia](#)

#### Question 2 of 264

You are called to a general medical ward during the night to review 48 year female who has become acutely agitated and confused. She came into hospital two days ago with a suspected urinary tract infection and has been making uneventful progress. She has a past history of traumatic spinal injury at level C5 three years ago with resulting spastic quadraparesis. On your arrival her blood pressure is 220/105 mmHg, heart rate is 55/min, and she is flushed and diaphoretic.

Of the following, what additional feature might you expect to find?

[Palpable bladder](#)55% [Ejection systolic murmur in the pulmonary area](#) 9% [Flushing of the skin in the trunk and legs](#)12% [Relative afferent pupillary defect](#)14% [Complete heart block](#)10%

This question is describing a case of autonomic dysreflexia. Of the options given, palpation of a distended bladder is likely and also diagnostic. Pulmonary murmurs can be a feature of the carcinoid syndrome. A relative afferent pupillary defect is seen with optic nerve pathology such as optic neuritis. Flushing of skin above the cord lesion is common due to parasympathetic feedback causing vasodilation but of course anything below the cord lesion remains vasoconstricted.

### **Autonomic dysreflexia**

This clinical syndrome occurs in patients who have had a spinal cord injury at, or above T6 spinal level. Briefly, afferent signals, most commonly triggered by faecal impaction or urinary retention (but many other triggers have been reported) cause a sympathetic spinal reflex via thoracolumbar outflow. The usual, centrally mediated, parasympathetic response however is prevented by the cord lesion. The result is an unbalanced physiological response, characterised by extreme hypertension, flushing and sweating above the level of the cord lesion, agitation, and in untreated cases severe consequences of extreme hypertension have been reported.

#### **Question 3 of 264**

A 23 year-old student with epilepsy presents with generalised tonic-clonic status epilepticus. He is already taking phenytoin. Despite intravenous administration of diazepam and then phenobarbital, he is still fitting after 30 minutes.

What is the best course of action?

[Check phenytoin levels and reload if necessary9%Send urine for toxicology6%Organise brain imaging6%Obtain an electroencephalogram \(EEG\)5%Induction of general anaesthesia with thiopentone75%](#)

### **Status epilepticus**

This is a medical emergency. The priority is termination of seizure activity, which if prolonged will lead to irreversible brain damage. First-line drugs are benzodiazepines such as diazepam or lorazepam. If ineffective within 10 minutes it is appropriate to start a second-line agent such as phenytoin, sodium valproate, levetiracetam, or phenobarbital. If no response within 30 minutes from onset, then the best way to achieve rapid control of seizure activity is induction of general anaesthesia.

#### Question 4 of 264

A 67-year-old male presents to your neurology clinic with his wife, reporting a 3-month history of worsening vision in his left eye. He is very reluctant to seek any medical help but says that a number of factors have finally convinced him to attend.

Over the past 2 months, he reports a constant and worsening headache, worse at night and with coughing. He has occasionally felt extremely nauseated and vomited on a number of occasions, at least twice waking him from sleep. His wife also notes significant personality change: her husband is a retired farmer who prides him on being a stoic man. She notes that he has become increasingly emotional and occasionally aggressive, which she puts down however to struggling with his symptoms. Prior to these symptoms starting 3 months ago, he has always been fit and well with no past medical or drug history.

On examination, you note a left relative afferent papillary defect with equally sized pupils. Visual acuity in the left eye is 6/60 and 6/9 on the right. Testing of colour vision with Ishihara plates demonstrates 0/17 on the left and 17/17 on the right. A central scotoma is found in the left eye. Fundoscopy of the left eye reveals a pale optic disc with poor vasculature while the right appears swollen. A full range of painless eye movements is demonstrated. The remaining examination of the cranial nerves, upper and lower limbs are unremarkable. Drops of blood are unremarkable, a MRI head is awaited.

What is the most likely diagnosis?

[Foster-Kennedy syndrome](#)59% [Idiopathic intracranial hypertension \(IIH\)](#)12% [Multiple sclerosis \(MS\)](#)10% [Frontotemporal dementia](#)12% [Age related macular degeneration \(ARMD\)](#)7%

This is a difficult question requiring recognition of a high-pressure headache, left optic atrophy and contralateral swollen disc secondary to papilloedema. The combination of an ipsilateral optic atrophy and contralateral papilloedema is an MRCP favourite: Foster-Kennedy syndrome, typically caused by a frontal lobe mass, normally a meningioma, which compressing on the ipsilateral optic nerve and olfactory nerve, while increasing intracranial pressure for the contralateral optic nerve sheath.

Idiopathic intracranial hypertension may present asymmetrically but typically produces bilateral disc swelling. It is conceivable the patient has multiple sclerosis with optic atrophy as a sequelae

of left optic neuritis, followed by a second episode of contralateral optic neuritis presenting as papillitis, inflammation of the optic nerve head. This is unlikely with only one episode of visual dysfunction described with an insidious progressive onset.

Frontotemporal dementia may explain the behavioural changes but does not account for visual symptoms.

Lastly, age-related macular degeneration can mimic papillitis on fundoscopy, with deposition of drusen making the optic disc 'look' swollen. However, the deposition of these retinal cell byproducts is generally more diffuse across the retina, with wet ARMD also displaying abnormal retinal vasculature. While retinal atrophy may be present, it does not typically produce optic atrophy.

### **Foster-Kennedy syndrome**

Foster-Kennedy syndrome describes a series of symptoms and signs associated with frontal lobe lesions.

#### **Features**

- optic atrophy in the ipsilateral eye
- papilloedema in the contralateral eye
- central scotoma in the ipsilateral eye
- anosmia

#### **Question 6 of 264**

A 63-year-old man presented with a three-week history of double vision and fatigue. Over this period he had noticed that when he swallowed liquids these often came back out of his nose. He reported a decreased exercise tolerance over the past six months due to fatigue and shortness of breath.

On examination he was thin. He had bilateral ptosis and diplopia on looking in multiple directions. His voice was soft and he appeared peripherally cyanosed. On auscultation his chest was clear and heart sounds were normal.

Observations:

- Heart rate: 90 beats per minute
- SaO<sub>2</sub>: 92% on room air
- Respiratory rate: 22 breaths per minute
- Temperature: 37.1 degrees Celsius
- Blood pressure: 110/68 mmHg

Arterial blood gases breathing air:

PO<sub>2</sub> 7.80 kPa (11.3 12.6)

PCO<sub>2</sub> 9.52 kPa (4.7 6.0)

pH 7.31 (7.35 7.45)

bicarbonate 32.4 mmol/L (21 29)

base excess 10 mmol/L (+/- 2)

Which urgent investigation should be performed next?

[Chest X-ray16%Forced vital capacity67%Computed Tomography Pulmonary Angiogram7%Electrocardiogram5%Bedside echocardiogram5%](#)

This patient has myasthenia gravis as suggested by his fatigue, ptosis, complex ophthalmoplegia and bulbar weakness. He has an element of neuromuscular weakness which is resulting in type 2 respiratory failure. The most important step after adequately resuscitating this patient is to perform a bedside Forced Vital Capacity measurement. If this is < 1.5 then it may be necessary to involve the Intensive Treatment Unit team and consider ventilatory support.

## **Myasthenia gravis**

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

## Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

## Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

## Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

## Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

## Question 7 of 264

A 65-year-old man underwent an elective inguinal hernia repair. Due to the list running late into the evening, the patient was admitted for an overnight stay. During the night after the operation the patient was observed to have an increasing oxygen requirement and the following morning was referred to the oncall medical registrar.

The patient reported feeling progressively more short of breath since the operation, particularly when he had tried to lie down to sleep. He denied any cough, chest pain, leg swelling or palpitations. Prior to the operation the patient had been generally well although he had found that he frequently experienced double vision when reading especially in the evening. He also had noticed some difficulties when chewing tough foods in recent weeks. Past medical history was unremarkable and the patient took no regular medications.

Examination revealed a regular pulse, no elevation of jugular venous pressure and normal heart sounds. Both calves were soft and non-tender. The patient had a shallow respiratory effort and was unable to speak in full sentences. Chest expansion was reduced bilaterally, chest was resonant with vesicular breath sounds throughout. The patient had bilateral weakness of facial muscles and ptosis on prolonged upward gaze. Power of neck flexion and extension was reduced, graded as 4/5.

Basic observations:

- Blood pressure: 120 / 76 mmHg
- Heart rate: 115 beats / min
- Respiratory rate: 32 breaths / min
- Temperature: 36.8°C

Portable CXR: technically poor film due to poor inspiratory effort; clear lung fields; no pleural effusion; no upper lobe blood diversion; no free air under diaphragm.

Arterial blood gas analysis (35 % O<sub>2</sub>)

pH	7.29
PaCO <sub>2</sub>	6.6 kPa
PaO <sub>2</sub>	8.7 kPa
Bicarbonate	18 mmol / L (reference 20.0-26.0)
Lactate	2.1 mmol / L

Bedside forced vital capacity: 1.9 L

What is the most important next step in management?

[Pyridostigmine15%](#)[Referral to intensive care unit48%](#)[Reduce percentage of supplemental oxygen5%](#)[High-dose corticosteroids8%](#)[Intravenous immunoglobulin24%](#)

The patient has symptoms and signs of previously unrecognised myasthenia gravis. The physiological stress of surgery has precipitated a myasthenic crisis associated with type 2 respiratory failure, tachycardia, tachypnoea and reduced forced vital capacity. The priority in management is to refer the patient to an intensive care unit for respiratory support.

Corticosteroids and pyridostigmine are mainstays of treatment of myasthenia gravis with intravenous immunoglobulin also used in severe cases. However, these treatments cannot be expected to restore respiratory muscle function rapidly in this emergency situation.

The patient has no history of obstructive lung disease with type 2 respiratory failure due instead to failure of ventilation due to respiratory muscle weakness. Therefore, reducing percentage of supplemental oxygen would not be beneficial and would cause additional hypoxia.

Spillane J, Higham E, Kullman D. Myasthenia gravis. BMJ 2012;345:e8497.

### **Myasthenia gravis: exacerbating factors**

The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of myasthenia gravis . Symptoms become more marked during the day

The following drugs may exacerbate myasthenia:

- penicillamine
- quinidine, procainamide
- beta-blockers
- lithium
- phenytoin
- antibiotics: gentamicin, macrolides, quinolones, tetracyclines

#### Question 8 of 264

A 32-year-old female presents with a 6-month history of progressive lower limb weakness and suprapubic tenderness. On examination, cranial nerves and upper limbs were unremarkable. You note 1/5 power in both lower limbs, hyperreflexic patella and ankle reflexes, bilateral clonus and upgoing plantar reflexes. The abdominal examination also revealed a suprapubic mass. After a urethral catheter was inserted, you note a residual volume of 1.8l. She is known to be HIV positive, diagnosed 8 years ago. Blood tests from an outpatient appointment revealed:

CMV IgG            positive  
EBV IgG            positive  
HTLV antibody positive



Hepatitis B      negative  
Hepatitis C      negative

An MRI spine is awaited. What is the most likely diagnosis?

[Tropical spastic paraparesis35%Spinal toxoplasmosis12%CMV transverse myelitis35%EBV transverse myelitis6%Tabes dorsalis12%](#)

This is a HIV and HTLV-1 positive patient presenting with paraparesis and urinary retention, a classic presentation of tropical spastic paraparesis. Toxoplasmosis in HIV patients typically presents in the brain, lungs or as a chorioretinitis. Transient viral inflammatory transverse myelitis by CMV and EBV typically resolves within 3 months, the presence of IgG in both suggest previous exposure and is of limited significance. Tabes dorsalis is a possibility but peripheral reflexes are typically lost with an extensor plantar reflex. Diagnosis of HTLV-1 tropical spastic paraparesis relies on a combination of clinical features and HTLV-1 load in serum and CSF. Treatments are limited, with steroids, presumably as an anti-inflammatory, producing only mild effects in a small population of patients.

## **Spastic paraparesis**

Spastic paraparesis describes a upper motor neuron pattern of weakness in the lower limbs

Causes

- demyelination e.g. multiple sclerosis
- cord compression: trauma, tumour
- parasagittal meningioma
- tropical spastic paraparesis
- transverse myelitis e.g. HIV
- syringomyelia
- hereditary spastic paraplegia
- osteoarthritis of the cervical spine

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A 45-year-old man complains of lower limb numbness associated with weakness. He also noted some recent problems with urinary incontinence and has recently attended the opticians due to some blurring of vision

On examination he has bilateral lower limb weakness (grade 3+/5). His tone was spastic on both sides with exaggerated reflexes. The planter reflexes were up-going bilaterally. The sensory level was at the tenth thoracic vertebra (T10). Eye examination revealed a normal visual acuity with a normal fundal examination.

He has a history of asthma and is currently well controlled with just a salbutamol inhaler.

Magnetic resonance imaging (MRI) of the brain is normal. MRI of the spine shows a hyper intense lesion spanning from (T7-T12). The following investigations had been ordered:

Na+	135 mmol/l
K+	4 mmol/l
Creatinine	80 µmol/l
Urea	4.5 mmol/l
CRP	5 mg/l
ESR	10 mm/hr
Urine analysis	Normal
ANA	Negative

Which one of the following investigations would be most useful to reach a diagnosis?

[Auditory evoked response potentials5%CSF analysis for oligoclonal bands18%Anti-aquaporin 4 antibodies55%Serum B1210%Visual evoked response potentials13%](#)

Neuromyelitis optica (Devic disease) should be suspected when the following is noted:

- quadriparesis or paraparesis within days to weeks
- vision changes
- normal brain MRI
- presence of anti-NMO antibodies (anti-aquaporin 4 antibodies)
- responsive to immunosuppressants

**Neuromyelitis optica**

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder. Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations<sup>1</sup>. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria<sup>2</sup>:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

1. Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805.

2. Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485.

#### Question 1 of 254

A 45-year-old teacher is reviewed in a routine nephrology clinic. She has end stage renal failure with focal segmental glomerular sclerosis (FSGS) on biopsy and is receiving renal replacement via haemodialysis. She requires hearing aids for bilateral sensorineural hearing loss and is of short stature. She mentions that she has been feeling more tired and lethargic in the last few months. A fasting blood sugar taken by her GP is 8.0mmol/l. She has a family history of diabetes in her mother and maternal grandmother, both of whom also required hearing aids at an early age. Given the above features, what is the most likely cause of her end stage renal failure?

[Autosomal dominant polycystic kidney disease4%Alport syndrome57%Liddle syndrome5%Maternally inherited diabetes and deafness \(MIDD\)30%Granulomatosis with polyangiitis \(Wegener granulomatosis\)4%](#)

Alport syndrome and GPA could also cause end stage renal failure and deafness. However, diabetes is not a feature of Alport syndrome and GPA is not a directly heritable disease.

ADPKD causes end stage renal failure with an autosomal dominant pattern of inheritance but would not explain the other features.

Liddle syndrome is a genetic cause of hypertension due to mutations in the epithelial sodium channel in the distal convoluted tubule.

## **Maternally inherited diabetes and deafness (MIDD)**

MIDD is a mitochondrial disease most commonly caused by the m.3243A>G mutation. The classical features are of sensorineural hearing loss and diabetes but a number of other systems can also be involved. It affects up to 1% of all patients with diabetes.

A hallmark of any mitochondrial disease is the maternal inheritance of the condition.

The same m.3243A>G mutation causes the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis and stroke-like symptoms) highlighting the variable presentation of different patients with the same mutation.

Clinical features include:

- Diabetes
- Sensorineural hearing loss
- Stroke-like symptoms
- Retinal dystrophy
- Proximal myopathy
- Cardiomyopathy, arrhythmias
- End stage renal failure - most often FSGS pattern on biopsy
- Short stature, low BMI

Question 4 of 254

A previously well 69 year old patient presents to the A+E department with a sudden onset of weakness. This was noticed by his wife who immediately called 999.

Neurological examination:

CN I-IV normal

CN V ophthalmic and maxillary divisions normal with reduced sensation in mandibular division on left side

CN VI normal

CN VII reduced power to left lower facial musculature

CN VIII normal

CN IX, X and XII weakness in swallow

CN XI weakness on turning the head to the left.

Right upper limb normal tone, power 5/5, normal reflexes and sensation. Normal finger pointing.  
Left upper limb markedly increased tone, power 1/5 globally in all muscle groups, brisk reflexes and reduced sensation to light touch. Unable to move limb to determine ability to finger pointing.

Right lower limb normal tone, power 5/5, normal reflexes and sensation. Heel-knee-shin test normal.

Left lower limb slightly increased tone, power 3/5 globally, brisk reflexes and reduced sensations. Reduced ability to heel-knee-shin test when compared to right side.

Gait - not assessed due to weakness.

Romberg's test - not done due to weakness.

[Left middle cerebral artery 9%](#)[Right middle cerebral artery 52%](#)[Posterior cerebral artery 16%](#)[Left anterior cerebral artery 7%](#)[Right anterior cerebral artery 17%](#)

The understanding of stroke territories is important both in clinical practice but also in the MRCP! In terms of limb weakness it must be remembered that an ischaemic event in the anterior cerebral territory caused contralateral hemiparesis (leg>arm) and the middle cerebral territory causes contralateral hemiparesis (face/arm>leg).

A posterior cerebral artery lesion causes contralateral homonymous hemianopia with amnesia and sensory loss.

## Stroke by anatomy

Site of the lesion	Associated effects
Anterior cerebral artery	Contralateral hemiparesis and sensory loss, lower extremity > upper
Middle cerebral artery	Contralateral hemiparesis and sensory loss, upper extremity > lower Contralateral homonymous hemianopia Aphasia
Posterior cerebral artery	Contralateral homonymous hemianopia with macular sparing Visual agnosia
Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain)	Ipsilateral CN III palsy Contralateral weakness of upper and lower extremity

Site of the lesion	Associated effects
Posterior inferior cerebellar artery (lateral medullary syndrome, Wallenberg syndrome)	Ipsilateral: facial pain and temperature loss Contralateral: limb/torso pain and temperature loss Ataxia, nystagmus
Anterior inferior cerebellar artery (lateral pontine syndrome)	Symptoms are similar to Wallenberg's (see above), but: Ipsilateral: facial paralysis and deafness
Retinal/ophthalmic artery	Amaurosis fugax
Basilar artery	'Locked-in' syndrome

#### Lacunar strokes

- present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia
- strong association with hypertension
- common sites include the basal ganglia, thalamus and internal capsule

#### Question 6 of 254

A 35-year-old lady was referred to the neurology clinic for investigation of facial weakness. Over the past 2 months, she noticed that her eyelids had tended to drop towards the end of the day, and she had occasional diplopia. She also felt that the corners of her mouth drooped a bit, and she reported some difficulty smiling. There was no limb weakness, and she had not had any difficulty swallowing.

On examination, there was a bilateral facial droop, and bilateral partial ptosis. She was sitting with her head tilted up to compensate for this. She had almost complete ptosis after trying to keep her eyes in elevation for more than 15 seconds. Eye movements were otherwise normal. Palatal movement was equal on both sides, and there were no abnormalities in tongue movements. Tone, power, reflexes and sensation were normal in the upper and lower limbs.

What is the most appropriate initial management?

[Mycophenolate mofetil6%](#)[Thymectomy7%](#)[Prednisolone14%](#)[Intravenous immunoglobulin11%](#)[Pyridostigmine63%](#)

This lady presents with weakness affecting her facial and extraocular muscles, demonstrating fatigability. This is characteristic of myasthenia gravis. Treatment choice depends on the severity of symptoms.

In mild disease such as in this case, acetylcholinesterase inhibitors such as pyridostigmine are useful in control of symptoms. In more severe disease, with limb weakness or bulbar dysfunction immunomodulatory agents are often required. Steroids are often employed, with the addition of steroid-sparing agents such as mycophenolate mofetil, ciclosporin or azathioprine if necessary.

Intravenous immunoglobulin and plasma exchange are useful in myasthenic crises. Thymectomy improves symptoms in cases associated with thymoma, and may also be beneficial in young patients with recent onset of symptoms, but would not be used as an initial treatment option.

## **Myasthenia gravis**

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

### Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

### Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies

- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

## Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

## Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

## Question 7 of 254

A 43-year-old gentleman is admitted to the Emergency Department with a 2-week history of worsening drowsiness and confusion. His wife states that he had initially complained of increased tiredness and had started taking to his bed immediately after arriving home from work. One week ago he stopped going to work altogether and his wife reports that he has been sleeping for most of the day since then. This morning she had difficulty waking him, and when she did manage to rouse him he seemed confused with apparent slurring of his speech.

His past medical history is remarkable for epilepsy and bipolar disorder.

On examination, he is responsive only to pain. His vital signs are within normal limits and examination of the chest is unremarkable. His abdomen is soft, with no obvious tenderness and no organomegaly. Bowel sounds are present.

A set of blood tests are taken:

Hb	152 g/l	Na <sup>+</sup>	139 mmol/l	Bilirubin	18 µmol/l
Platelets	278 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.3 mmol/l	ALP	117 u/l
WBC	8.1 * 10 <sup>9</sup> /l	Urea	5.2 mmol/l	ALT	19 u/l
Neuts	5.4 * 10 <sup>9</sup> /l	Creatinine	93 µmol/l	γGT	48 u/l
Lymphs	1.8 * 10 <sup>9</sup> /l			Albumin	41 g/l
Eosin	0.2 * 10 <sup>9</sup> /l			Ammonia	197 µmol/l



His wife later remarks that his medications have recently been altered by his GP. Which of the following is most likely to be responsible?

[Lithium26% Sodium valproate32% Venlafaxine14% Diazepam11% Quetiapine17%](#)

The patient's presenting symptoms are relatively non-specific and, taken in high enough doses, any of the medications listed could cause impairment of consciousness. The patient's grossly abnormal ammonia level is the critical detail in this case and confirms a diagnosis of valproate-associated hyperammonaemic encephalopathy (VHE).

VHE is a well-documented complication of valproate therapy and can occur in patients with therapeutic as well supratherapeutic plasma valproate levels. Valproate inhibits carbamoyl phosphate synthetase I, an enzyme essential for ammonia metabolism in the liver, leading to elevated plasma ammonium levels. Interestingly, asymptomatic hyperammonaemia has been shown to occur in a large proportion of patients taking sodium valproate.

Reference: Wadzinski, J., Franks, R., Roane, D. and Bayard, M. (2007). Valproate-associated Hyperammonemic Encephalopathy. The Journal of the American Board of Family Medicine, 20(5), pp.499-502.

## **Sodium valproate**

Sodium valproate is used in the management of epilepsy and is first line therapy for generalised seizures. It works by increasing GABA activity.

### **Adverse effects**

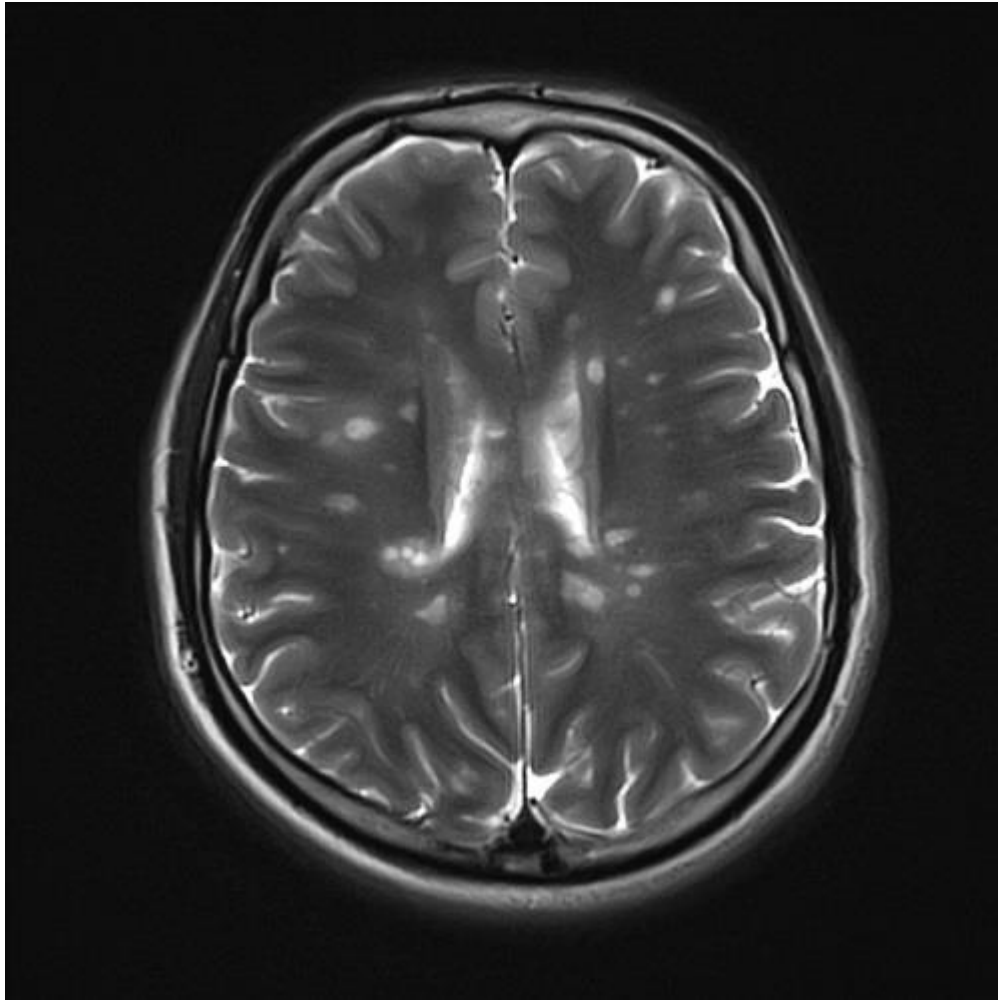
- gastrointestinal: nausea
- increased appetite and weight gain
- alopecia: regrowth may be curly
- ataxia
- tremor
- hepatitis
- pancreatitis
- thrombocytopaenia
- teratogenic
- hyponatraemia

A 24-year-old man is referred to the neurology clinic by his GP. He describes a four month history of left-sided numbness and intermittent tingling. This mainly affects his left arm but he occasionally has symptoms in the left leg. There is no history of headaches, visual problems or weakness.

His GP has performed a series of blood tests including a full blood count, urea and electrolytes, vitamin B12 and C reactive protein, all of which were normal.

Neurological examination today was normal other than reduced sensation in the left C6/7 dermatome.

A MRI head is performed. The T2 images are shown below:



© Image used on license from [Radiopaedia](#)



What is the most likely diagnosis?

[Creutzfeldt-Jakob disease](#)8% [Multiple sclerosis](#)60% [Adrenoleucodystrophy](#)13% [Cerebral toxoplasmosis](#)13% [Glioblastoma multiforme](#)5%

The MRI scan is consistent with multiple sclerosis. Widespread periventricular, juxtacortical, post fossa and upper cervical cord high T2 regions are noted. Note the difference in the lesions with varying degrees of contrast enhancement and restricted diffusion indicating active/recent demyelination. This satisfies the diagnostic criteria in terms of separation in terms of time space.

### **Multiple sclerosis: investigation**

Diagnosis requires demonstration of lesions disseminated in time and space

#### **MRI**

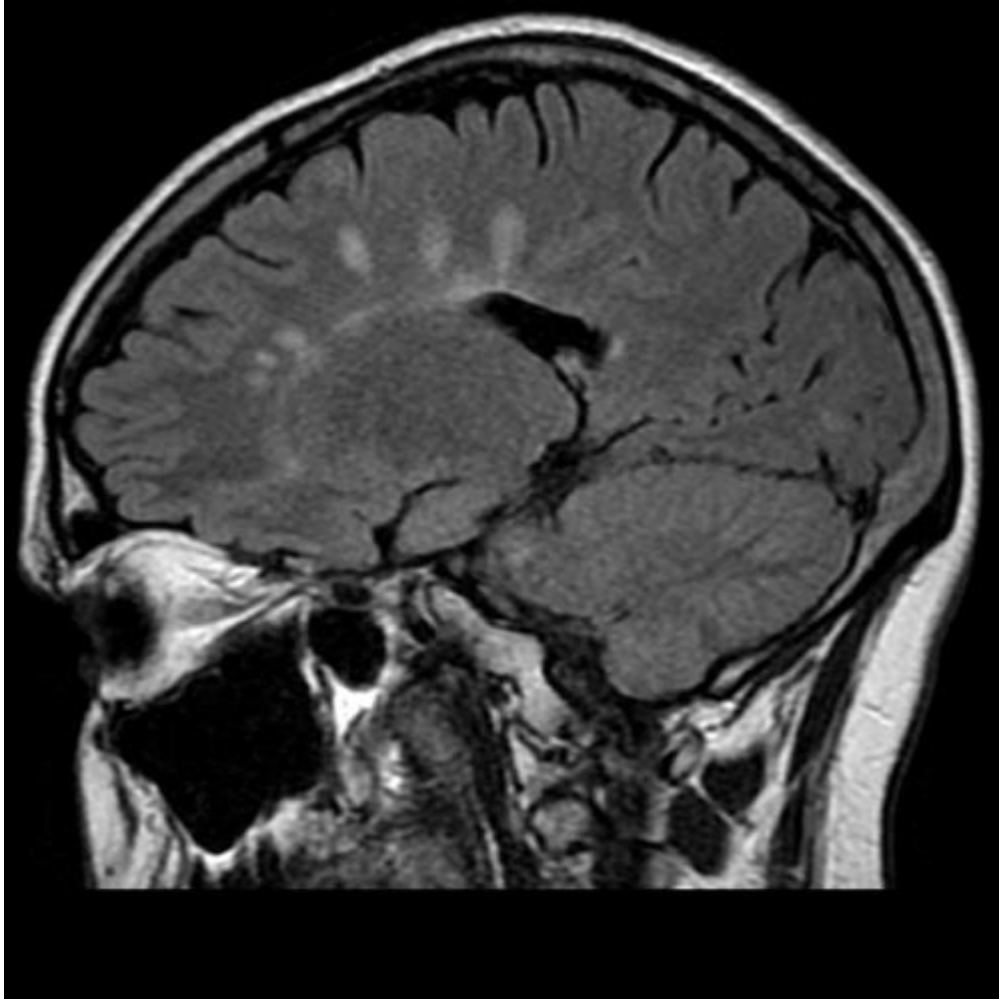
- high signal T2 lesions
- periventricular plaques
- Dawson fingers: often seen on FLAIR images - hyperintense lesions perpendicular to the corpus callosum

#### **CSF**

- oligoclonal bands (and not in serum)
- increased intrathecal synthesis of IgG

#### **Visual evoked potentials**

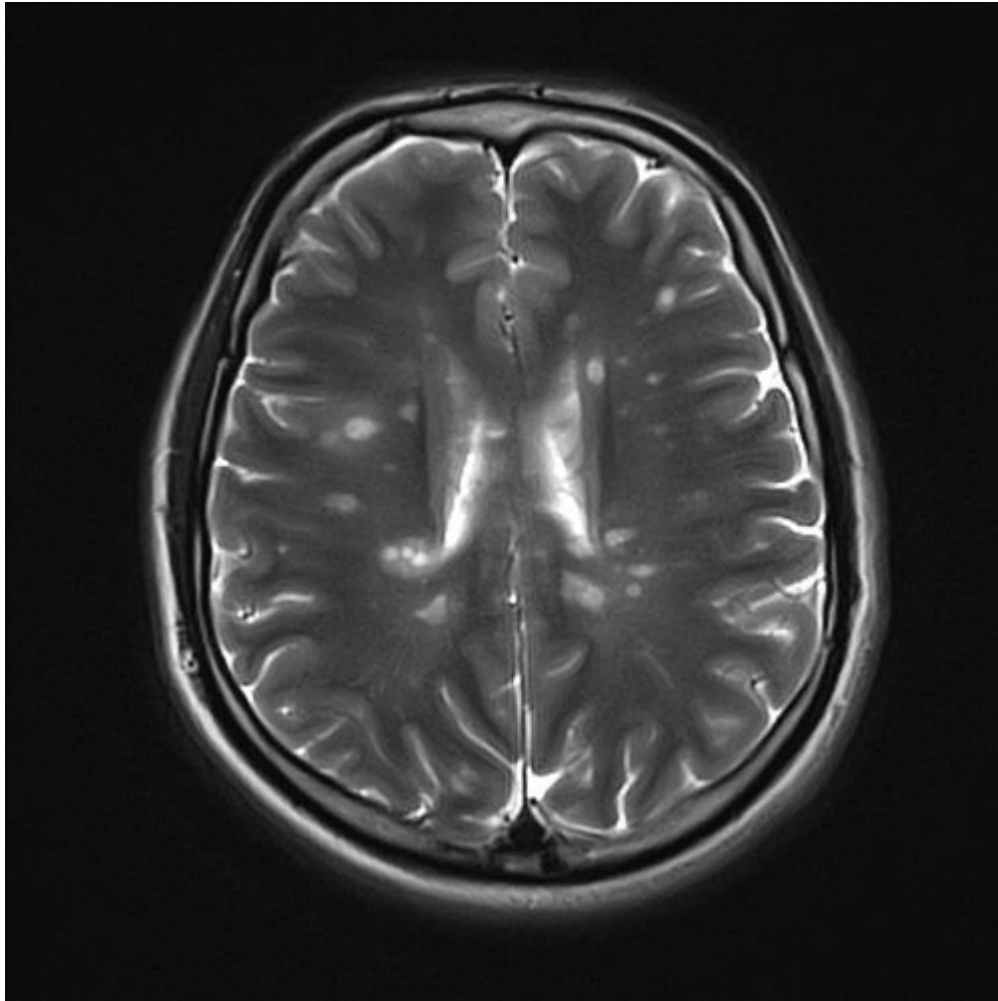
- delayed, but well preserved waveform



© Image used on license from [Radiopaedia](#)



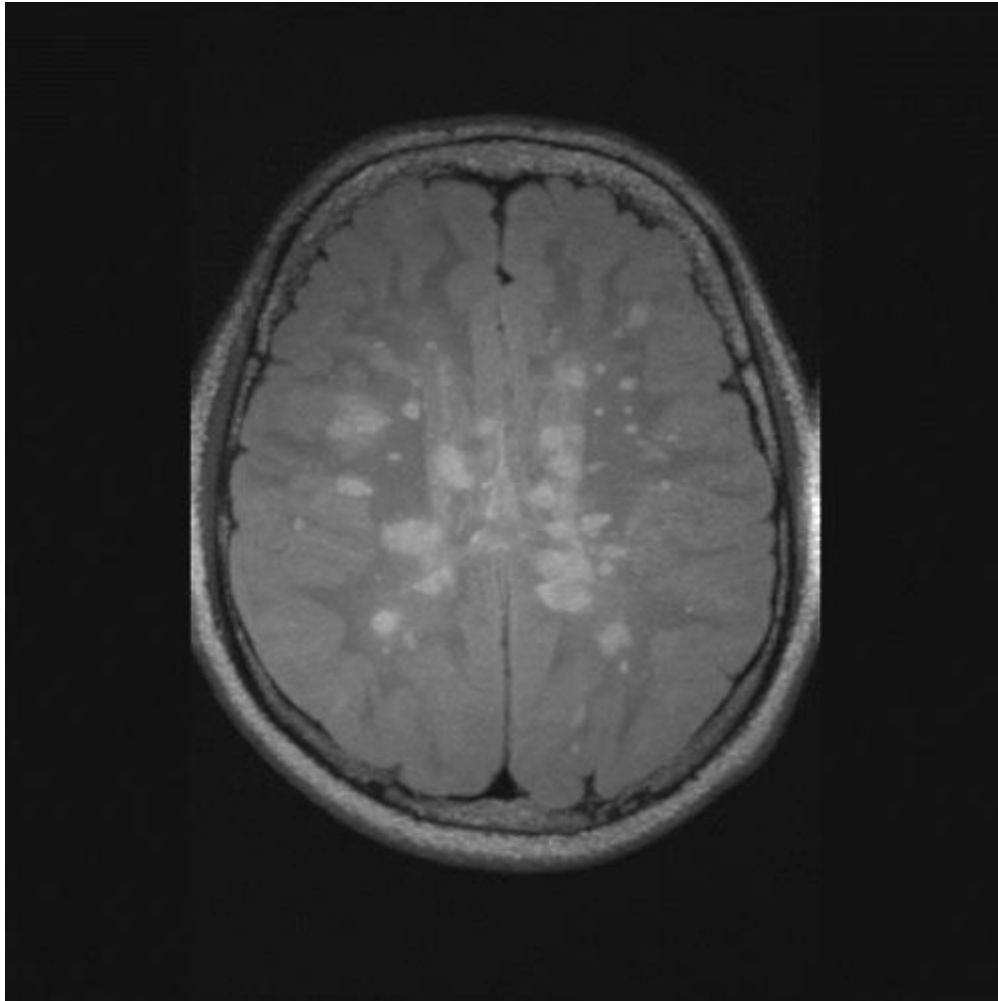
MRI showing multiple white matter plaques penpendicular to the corpus callosum giving the appearance of Dawson fingers



© Image used on license from [Radiopaedia](#)



MRI from a young patient with multiple sclerosis. Widespread periventricular, juxtacortical, post fossa and upper cervical cord high T2 regions are noted. Note the difference in the lesions with varying degrees of contrast enhancement and restricted diffusion indicating active/recent demyelination. This satisfies the diagnostic criteria in terms of separation in terms of time space.



© Image used on license from [Radiopaedia](#)



MRI FLAIR from the same patient as above. The numerous lesions are more easily identified than in the above T2 image.

#### Question 1 of 244

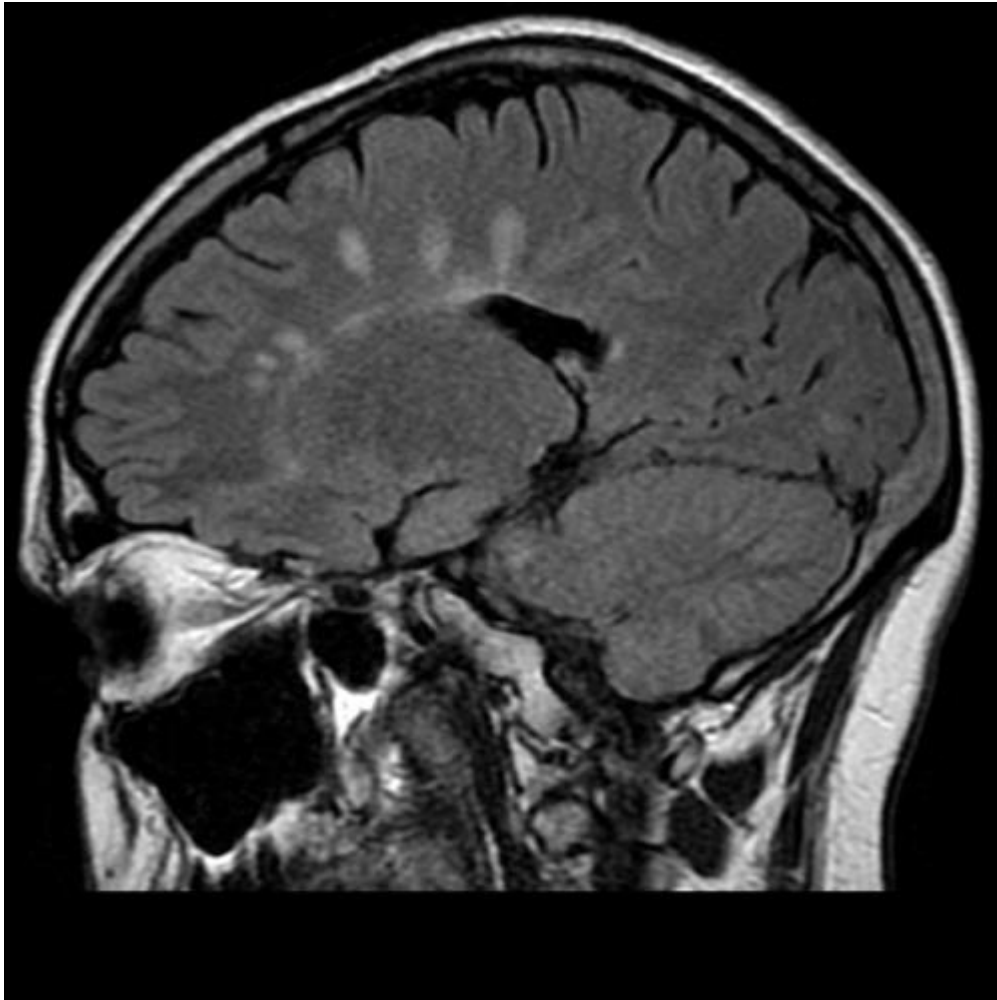
A 31-year-old woman is reviewed in the neurology clinic. For the past 6 months she has been presenting to her GP with a variety of symptoms including lethargy, heat intolerance, pins/needles and limb numbness. For the past 4 weeks she has also been complaining of shooting pains in her right hand.

Her GP has arranged a number of blood tests including thyroid function tests and vitamin B12 which

were reported as normal.

A neurological examination today demonstrates no consistent neurological findings.

A MRI is requested:



© Image used on license from [Radiopaedia](#)



What is the most likely diagnosis?

[Multiple sclerosis](#)70% [Pituitary tumour](#)7% [Ependymoma](#)8% [Acute disseminated encephalomyelitis \(ADEM\)](#)11% [Systemic lupus erythematosus](#)4%

The MRI shows multiple white matter plaques perpendicular to the corpus callosum giving the appearance of Dawson fingers - a classic MRI finding in multiple sclerosis.

Lethargy is a clue in this question. It is very common feature in patients with multiple sclerosis. Other features such as pain and heat intolerance and also seen.

## **Multiple sclerosis: investigation**

Diagnosis requires demonstration of lesions disseminated in time and space

### **MRI**

- high signal T2 lesions
- periventricular plaques
- Dawson fingers: often seen on FLAIR images - hyperintense lesions perpendicular to the corpus callosum

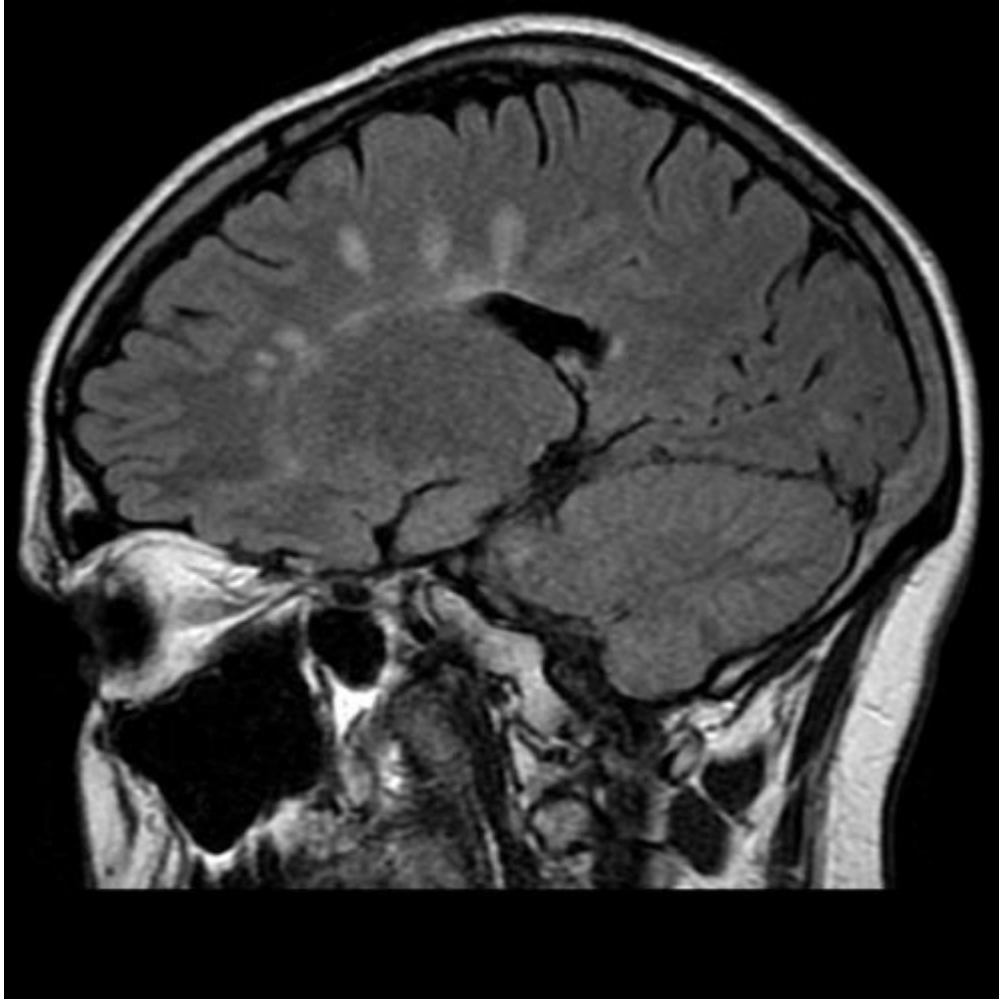
### **CSF**

- oligoclonal bands (and not in serum)
- increased intrathecal synthesis of IgG

### **Visual evoked potentials**

- delayed, but well preserved waveform

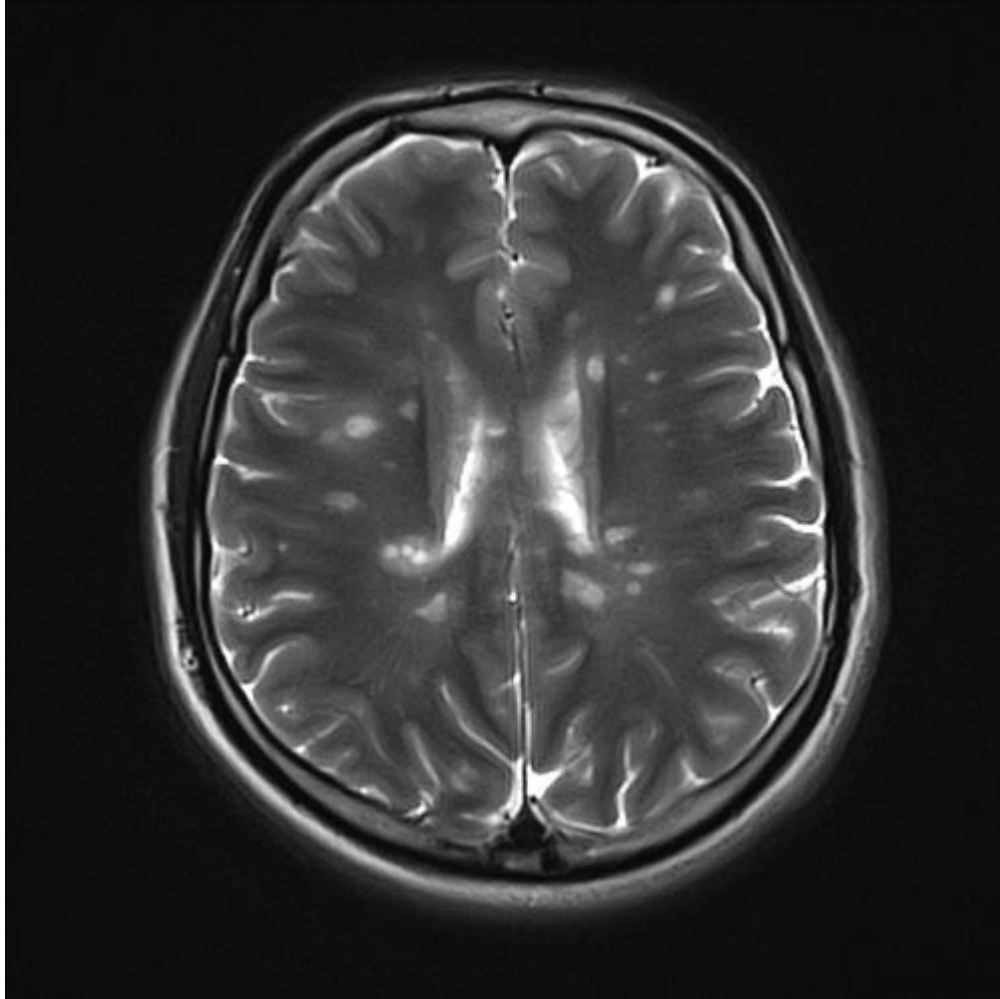




© Image used on license from [Radiopaedia](#)



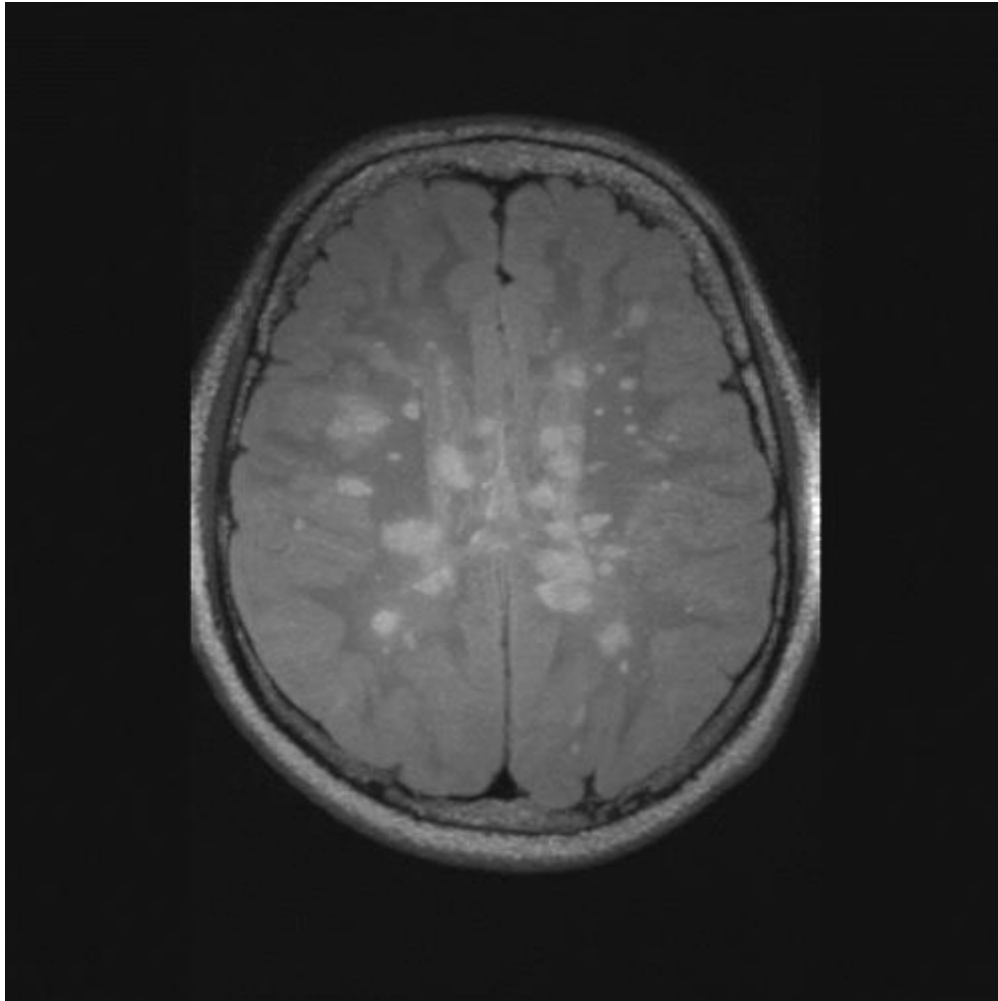
MRI showing multiple white matter plaques perpendicular to the corpus callosum giving the appearance of Dawson fingers



© Image used on license from [Radiopaedia](#)



MRI from a young patient with multiple sclerosis. Widespread periventricular, juxtacortical, post fossa and upper cervical cord high T2 regions are noted. Note the difference in the lesions with varying degrees of contrast enhancement and restricted diffusion indicating active/recent demyelination. This satisfies the diagnostic criteria in terms of separation in terms of time space.



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



MRI FLAIR from the same patient as above. The numerous lesions are more easily identified than in the above T2 image.

#### Question 2 of 244

A 32-year-old lady develops a progressive loss of central vision in both eyes over two days. Her eyes are also painful to move. 24 hours later she develops additional paraesthesia in both arms with an associated weakness of both arms. On examination, she has central scotoma of both eyes. She also has a 3/5 global weakness of both arms with hyperreflexia and patchy sensory loss. In the following days, this progresses to paraesthesia and weakness in both lower limbs plus extensor plantar responses. Raised serum levels of which of the following would be most helpful

in establishing the suspected underlying diagnosis? helpful in establishing the suspected diagnosis?

Anti-Hu antibodies 11% Antinuclear antibodies 6% N-methyl-d-aspartate (NMDA) receptor antibodies 18% Anti-Aquaporin-4 antibodies 55% Voltage gated potassium channel antibodies 10%

The diagnosis is neuromyelitis optica (NMO). Its features are best remembered by what they describe: the co-occurrence of optic neuritis and myelitis. Myelitis describes swelling of the spinal cord and in NMO it characteristically extends over three or more vertebral segments, and the limb features correspond to the level affected. The optic neuritis in NMO is bilateral.

The clinical course of NMO is variable. It may occur as a monophasic illness that is either fulminant and fatal or associated with varying degrees of recovery. Polyphasic courses characterised by relapses and remissions also occur.

A curative treatment for NMO does not exist to date and management, like in MS, focuses on remission and prevention of relapse.

Treatment of an acute attack is with steroids: 5 days of IV methylprednisolone at a dose of 1g, followed by an oral steroid taper. Maintenance therapy is normally with azathioprine, rituximab, or mycophenolate mofetil.

## **Neuromyelitis optica**

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder. Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations<sup>1</sup>. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria<sup>2</sup>:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

1. Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805.

2. Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485.

### Question 3 of 244

A 55-year-old woman attends neurology clinic for follow-up. At her first appointment 6 months previously, a clinical diagnosis of trigeminal neuralgia had been made and treatment with carbamazepine initiated. During clinic review the patient complained of ongoing symptoms with only limited benefit from drug treatment.

On her previous assessment, the patient had reported pain episodes associated with the cheek and jaw of the right side of her face. Subsequently, in addition to similar ongoing episodes, the patient had suffered from two episodes of pain affecting the forehead and peri-orbital region on the left side of her face. On one occasion, she had suffered from both right and left sided pain at the same time. She reported that the carbamazepine treatment had initially reduced the intensity of the pain episodes by perhaps 50 %, but that the severity of recent attacks had again worsened to their original level. When her drug history was checked, it was apparent that the carbamazepine dose had been titrated up appropriately by the patients GP.

The patient also stated that following her previous clinic appointment she had been discussing the situation with her sister, who had reminded the patient that their mother had suffered several episodes of visual loss during her life but had not undergone any medical investigation.

Cranial nerve examination demonstrated normal eye movements and pupillary responses. There was no evidence of facial nerve weakness, however a subjective numbness of sensation was noted in the left cheek region (this had not been noted on previous examination in clinic). There were no lesions around the head and neck or inside the mouth. Peripheral neurological examination was remarkable for borderline dysdiadochokinesia in the right upper limb and a positive Babinski response in the right lower limb.

What is the most appropriate investigation for this patient?

[Visual evoked potentials9%](#)[Three-plane fine-slice MRI brain with contrast31%](#)[CSF oligoclonal bands11%](#)[CT brain with contrast6%](#)[Standard protocol MRI brain with contrast43%](#)

The patients previous clinical diagnosis of trigeminal neuralgia clearly needs to be reviewed in light of several red-flag features. In particular, the limited response to carbamazepine, the occurrence of simultaneous bilateral pain and the history of pain associated with the ophthalmic division are inconsistent with a typical presentation of trigeminal neuralgia. Moreover, the patient has developed some soft neurological signs that are suggestive of CNS lesions in various areas of the brain.

Multiple sclerosis is the most likely alternative diagnosis, although other causes of trigeminal pain such as space occupying lesions, malignant invasion of the trigeminal nerve or thalamic infarction are also possibilities. The best investigation to assess for all these differentials is standard protocol MRI brain with contrast. Demyelination or trigeminal nerve infiltration would not be reliably noted on CT brain with contrast making this less likely to progress the diagnosis. Visual evoked potentials and CSF oligoclonal bands are other investigations that may support a diagnosis of multiple sclerosis but would not confirm or refute this diagnosis in isolation.

Typical cases of trigeminal neuralgia are considered to result from contact between blood vessels and the trigeminal nerve. Such vascular contacts can be observed on specialised MRI protocols requiring fine-slicing in three-planes. However, given the additional expense and the fact that such contacts can be a normal variant, this investigation is not normally performed. A standard protocol MRI brain is sufficient to assess for the important differentials of trigeminal neuralgia discussed above.

Zakrzewska J, Linskey M. Trigeminal neuralgia. BMJ 2014;348:g474.

## **Trigeminal neuralgia**

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur

The International Headache Society defines trigeminal neuralgia as:

- a unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
- the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- the pains usually remit for variable periods

## **Management**

- carbamazepine is first-line
- failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

## **Question 1 of 241**

A 55-year-old female presents with 3 weeks of bilateral tingling sensation in her medial one and half digits at night. She has noted a clawing of her 4th and 5th digits and she is particularly

concerned by the cosmetic elements. She also complains of a left sided foot drop present over the past 8 months. Her past medical history includes type 2 diabetes mellitus, for which she takes metformin 850mg TDS and she admits to occasional poor compliance. Her last HbA1c was 53 mmol/mol. She has also had multiple admissions for surgery to her feet at childhood but she is unaware of further details. She was adopted and is unaware of her birth family history. On examination, she clinically has a left common peroneal palsy with bilateral thin calves, and loss of sensation in bilateral ulnar nerve territories. What is the unifying diagnosis for her presenting paraesthesia and foot drop?

[Hereditary neuropathy with liability to pressure palsies 50%](#) [Diabetic neuropathy 10%](#) [Chronic inflammation demyelinating polyneuropathy \(CIDP\) 31%](#) [Systemic lupus erythematosus \(SLE\) 4%](#) [Sarcoidosis 4%](#)

The patient has thin calves and previous foot deformities requiring surgery, suggestive of Charcot-Marie-Tooth disease or hereditary motor sensory neuropathy (HSMN), a disorder caused by deletion in the PMP22 gene, the same gene mutation responsible for hereditary neuropathy with liability to pressure palsies. Common peroneal nerve is the most commonly affected nerve (36%) followed by the ulnar nerve (28%). Diagnosis is confirmed by genetic testing.

1. Mouton P, Tardieu S, Gouider R et al. Spectrum of clinical and electrophysiologic features in HNPP patients with the 17p11.2 deletion. *Neurology*. 1999;52(7):1440

## **HSMN**

Hereditary sensorimotor neuropathy (HSMN) is a relatively new term which encompasses Charcot-Marie-Tooth disease (also known as peroneal muscular atrophy). Over 7 types have been characterised - however only 2 are common to clinical practice

- HSMN type I: primarily due to demyelinating pathology
- HSMN type II: primarily due to axonal pathology

### **HSMN type I**

- autosomal dominant
- due to defect in PMP-22 gene (which codes for myelin)
- features often start at puberty
- motor symptoms predominate
- distal muscle wasting, pes cavus, clawed toes
- foot drop, leg weakness often first features

### Question 2 of 241

A 43-year-old female presents with a second episode of loss of sensation in her left anterior thigh and right foot. This is her second episode within the past four months. She had recently reported an episode of left anterior shin numbness 1 year ago when an MRI with gadolinium demonstrated 'spots in her spinal cord' and she was diagnosed with transverse myelitis. Her past medical history also includes ulcerative colitis, diagnosed aged 27 years old and primary sclerosing cholangitis. Her serum tests are as follows:

Hb 125 g/l

Platelets  $274 \times 10^9/l$

WBC  $7.5 \times 10^9/l$

Na<sup>+</sup> 139 mmol/l

K<sup>+</sup> 4.4 mmol/l

Urea 4.7 mmol/l

Creatinine 78  $\mu\text{mol/l}$

Bilirubin 49  $\mu\text{mol/l}$

ALP 305 u/l

ALT 180 u/l

You commence five days of high dose oral methylprednisolone. What is the most appropriate next management?

[Interferon beta43%Glatiramer acetate25%Fingolimod11%Natalizumab16%Mitoxantrone6%](#)

The patient presents with a clear history of recurrent relapses of relapsing-remitting multiple sclerosis (RRMS), isolated in time and location. In addition, NICE recommends that any patient experiencing more than two debilitating episodes of RRMS be considered for disease modifying therapies.

A number of 1st line disease modifying therapies are available and the choice is made on a patient-by-patient basis. Interferon beta 1a, beta 1b, glatiramer acetate, diethyl fumarate and teriflunomide are all valid choices. However, deranged liver function is contraindicated in the use of interferons, as in this case, where the patient has a cholestatic pattern of liver dysfunction secondary to primary sclerosing cholangitis. Glatiramer acetate is not contraindicated in liver dysfunction and hence the only suitable choice.

Fingolimod is a sphingosine 1 phosphate receptor modulator affecting lymphocyte migration that has been proven to reduce the number of relapses and slow the rate of number of new MRI lesions. However, it was also associated with increased incidence of varicella zoster, tumour formation and progressive multifocal leucoencephalopathy (PML), another demyelinating central nervous system condition. As a result, fingolimod is reserved for patients who fail 1st line



therapies. Similarly, while natalizumab is effective in modifying multiple sclerosis progression, it is also associated with PML and not considered a 1st line treatment. Mitoxantrone is a chemotherapy agent that inhibits DNA synthesis and repair, associated with significant cardiotoxicity, reserved only for RRMS patients who have failed other therapies with rapidly progressive disease.

## **Multiple sclerosis: management**

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

### **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

### **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

## **Some specific problems**

Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

### Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

### Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying
  - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

### Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line

### Question 3 of 241

An 81-year-old lady with a history of congestive cardiac failure was assessed in accident and emergency and clinically diagnosed with an acute ischaemic stroke. Her main deficits were slurred speech and left sided facial droop with some loss of fine motor control in the left hand. On admission, her blood pressure was 185/70mmHg with a heart rate of 95 beats per minute in sinus rhythm.

The initial CT scan of her brain showed some evidence of chronic small vessel ischaemia, but no acute pathology, in particular no haemorrhage was seen. Which of the following combinations of investigations should be carried out during the acute admission?

[MRI, transthoracic echocardiogram \(TTE\), cardiac telemetry and carotid duplex study 63% Transoesophageal echocardiogram \(TOE\), CT cerebral angiogram and carotid duplex study 16% CT scan, fasting lipids and a video fluoroscopy swallow study 9% Fasting glucose,](#)

## Electroencephalogram (EEG), MRI and thrombophilia screen 5% Thrombophilia screen, MRI and a TTE7%

After a diagnosis of ischaemic stroke is suspected based on clinical assessment and the absence of haemorrhage on CT scan, a number of further investigations should be requested in order to confirm the diagnosis and determine the underlying aetiology of the stroke.

- MRI is the most sensitive and specific modality for identifying an acute ischaemic stroke using diffusion-weighted imaging (DWI). If MRI is unavailable or a patient is ineligible to undergo an MRI, a serial CT scan may show interval changes consistent with an evolving ischaemic stroke.
- The remaining investigations should serve to localise the focus of thrombus or atheroma that has caused the stroke, but importantly, only investigations that will lead to a change in management are necessary. These include a carotid duplex study and/or CT carotid angiogram, a transthoracic echocardiogram (TTE) and cardiac telemetry.
- The carotid studies may identify a relevant significant stenosis necessitating carotid endarterectomy
- The TTE may identify an intraventricular thrombus, valvular pathology or mass that is the cause for thromboembolic stroke necessitating further investigation or the initiation of anticoagulation
- The cardiac telemetry may identify atrial fibrillation requiring consideration of anticoagulation.
- In addition, the above investigations fasting lipids should be measured as well as fasting glucose and or HbA1c in TIA/stroke patients.

A thrombophilia screen or TOE are not required routinely but may be requested in certain patients. A CT cerebral angiogram is needed in some circumstances, but not currently required for the routine investigation of ischaemic stroke.

## **Stroke: management**

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is  $> 3.5$  mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

Absolute	Relative
<ul style="list-style-type: none"> <li>- Previous intracranial haemorrhage</li> <li>- Seizure at onset of stroke</li> <li>- Intracranial neoplasm</li> <li>- Suspected subarachnoid haemorrhage</li> <li>- Stroke or traumatic brain injury in preceding 3 months</li> <li>- Lumbar puncture in preceding 7 days</li> <li>- Gastrointestinal haemorrhage in preceding 3 weeks</li> <li>- Active bleeding</li> <li>- Pregnancy</li> <li>- Oesophageal varices</li> <li>- Uncontrolled hypertension <math>&gt;200/120</math>mmHg</li> </ul>	<ul style="list-style-type: none"> <li>- Concurrent anticoagulation (INR <math>&gt;1.7</math>)</li> <li>- Haemorrhagic diathesis</li> <li>- Active diabetic haemorrhagic retinopathy</li> <li>- Suspected intracardiac thrombus</li> <li>- Major surgery / trauma in preceding 2 weeks</li> </ul>

## Secondary prevention

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

#### Question 1 of 238

A 46-year-old female presents with her third episode of diplopia in two years. During the first episode 3 years ago, her medical notes record that she was unable to abduct her left eye and had a left partial ptosis, which in subsequent clinic follow-up was found to have been resolved after 4 weeks. Her second episode occurred 6 months ago, during which she experienced mild vertical diplopia, diagnosed by GP as a fourth nerve palsy secondary to diabetic microvascular disease, which improved to normal after 6 weeks.

Her past medical history includes insulin dependent diabetes, with moderate control HbA1c (IFCC 39 mmol/mol), autoimmune hypothyroidism and vitiligo. She is a non-smoker. On examination today, you note a failure of vertical upgaze in her right eye and 50% failure of adduction with a 50% partial ptosis. Both pupils were equal and reactive.

Her admission blood tests were unremarkable. An MRI head and orbits demonstrated no orbital or intracranial pathology. Which of the following history is most likely to produce the underlying diagnosis?

[Single fibre EMG33% Lumbar puncture including oligoclonal bands24% Neurogenetics15% CT chest/abdomen/pelvis9% ANA, ANCA, complement autoimmune screen19%](#)

The first key to the question is realisation that the patient has presented with a relapsing-remitting course of a disorder. This clinical course points against a progressive degenerative or underlying genetic disorder causing ophthalmoplegia (e.g. Kearns-Sayre, NARP) and a paraneoplastic syndrome, hence a CT chest/abdomen/pelvis investigating for a primary malignancy would be unhelpful.

Secondly, the ophthalmoplegia is caused by ocular paresis unexplained by a single cranial nerve, pointing the site of lesion towards either the neuromuscular junction or individual nerves e.g. mononeuritis multiplex. The involvement of ocular nerves only without systemic symptoms would be extremely unlikely for a systemic autoimmune disease causing mononeuritis multiplex; the patient's diabetic control is actually very good, again making this diagnosis less likely.

The third learning point is that ocular and generalised myasthenia gravis does NOT necessarily present symmetrically. The diagnosis is made either with anti-acetylcholine receptor antibodies or anti muscle-specific kinase (anti-MUSK) antibodies but note their significantly lower sensitivity in ocular myasthenia compared to generalised myasthenia. Single fibre EMG examines temporal abnormalities in single motor nerve firing from a single motor unit, called 'jitter', in the orbicularis oculi and superior rectus levator palpebrae muscle. This is particularly sensitive in diagnosing ocular myasthenia, with sensitivities of up to 95%.

## **Myasthenia gravis**

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

## **Associations**

- thymomas in 15%

- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

### Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

### Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

### Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

### \Question 3 of 238

You see a 46 year-old man who has been referred by his GP to the neurology clinic.

He gives a one year history of facial pain. The pain particularly comes on when he is shaving or brushing his teeth, and he describes it as 'stabbing' through the teeth of his upper jaw and over the left side of his face. He has seen a succession of dentists and had several teeth removed, with no relief. The pain has been getting progressively worse, and whereas before it occurred in discrete attacks, it now occurs almost all the time. He has read several online sources and has become convinced that he has a brain tumour, which has led to him becoming depressed and withdrawn.

His past medical history includes essential hypertension, for which he takes perindopril. He also suffers from sinusitis, and has had a sinus washout on more than one occasion. Two years ago whilst on a business trip abroad he had a problem with the vision in his right eye, which spontaneously resolved over a few weeks, and for which he sought no treatment.

General examination is unremarkable. Cranial nerve examination is largely normal but you notice that there is a patch of numbness over the left cheek. Power is 5/5 across all muscle groups in the limbs, reflexes are normal, and plantars are downgoing. Sensation in the limbs is normal.

What is the most appropriate course of action?

[Reassure him he has trigeminal neuralgia, for which unfortunately there is no treatment4% Reassure him he has trigeminal neuralgia, and start carbamazepine 300mg daily37% Refer to the neurosurgeons for microvascular decompression12% Perform MR head with gadolinium contrast40% Perform CT head with contrast8%](#)

This man needs investigation before any further management is considered. He has pain which is typical for trigeminal neuralgia. However, objective sensory loss does not occur in idiopathic trigeminal neuralgia and is highly suggestive of an underlying cause. This may occur due to compression of the trigeminal nerve by a space-occupying lesion such as a tumour, or by a demyelinating plaque of multiple sclerosis affecting the trigeminal root at the pons. The episode of transient unilateral visual disturbance that this man suffered two years ago raises the possibility of optic neuritis, and thus the history is suspicious for MS. Malignancy is also a distinct possibility. Gadolinium-enhanced MR of the head is the best investigation to detect both.

Carbamazepine is an effective treatment for trigeminal neuralgia and produces at least some response in 70% of patients. Neurosurgical options such as microvascular decompression are considered only once medical options have been exhausted.

## **Trigeminal neuralgia**

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur

The International Headache Society defines trigeminal neuralgia as:

- a unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve



- the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- the pains usually remit for variable periods

## Management

- carbamazepine is first-line
- failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

Question 4 of 238

A 27-year-old caucasian woman is 28 weeks pregnant. She has been epileptic since the age of 7 and takes lamotrigine, which she has continued throughout the pregnancy. She has not had a seizure for 2 years. What must you consider in pregnant patients taking lamotrigine?

[Serum lamotrigine levels fall in the second trimester34%](#)[She must not breastfeed while taking lamotrigine12%](#)[She should be advised to stop lamotrigine6%](#)[Folic acid 400mcg should be taken throughout pregnancy29%](#)[It is protein bound and therefore drug levels increase in pregnancy18%](#)

Due to the increased plasma volume and enhanced renal/hepatic drug clearance, lamotrigine levels decrease in the second trimester of pregnancy. It may be necessary to increase the dose of lamotrigine at this time (normally increased two or three fold). A baseline serum drug level is useful to establish compliance and inform future changes in drug doses.

Breastfeeding is not contraindicated in women taking lamotrigine. However, the infant should be monitored for signs of accumulation such as a rash or drowsiness.

Patients should not stop their anti-epileptic medications unless a joint decision has been made in conjunction with an obstetrician/obstetric physician doctor. If a patient has been seizure-free for >2 years and is on dual therapy then it may be beneficial to reduce/stop one of the medications.

Patients on anti-epileptic medications should take folic acid 5mg throughout pregnancy.

Lamotrigine has low levels of protein binding and therefore is not affected by the decreased serum protein levels in pregnancy.

Further reading:

## **Epilepsy: pregnancy and breast feeding**

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus. All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy to minimise the risk of neural tube defects. Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

### **Other points**

- aim for monotherapy
- there is no indication to monitor antiepileptic drug levels
- sodium valproate: associated with neural tube defects
- carbamazepine: often considered the least teratogenic of the older antiepileptics
- phenytoin: associated with cleft palate
- lamotrigine: studies to date suggest the rate of congenital malformations may be low. The dose of lamotrigine may need to be increased in pregnancy

Breast feeding is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn

## **Sodium valproate**

The November 2013 issue of the Drug Safety Update also carried a warning about new evidence showing a significant risk of neurodevelopmental delay in children following maternal use of sodium valproate.

The update concludes that sodium valproate should not be used during pregnancy and in women of childbearing age unless clearly necessary. Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.

### Question 5 of 238

A 43-year-old man is apprehended by the police after a violent assault outside a pub. He is brought to the attention of the duty psychiatrist because he is extremely confused and agitated. He repeatedly says that his wife is having an affair with the Prime Minister. He believes this to be true because of a message encoded in the traffic lights. He also mentions that he has not slept in the last two days.

The psychiatric assessment is interrupted when he has a tonic-clonic seizure, which self-terminates in 3 minutes. He is taken to the local Accident and Emergency department and reviewed by the medical team.

The medical SHO manages to contact his wife, who reports that he is normally fit and well and she last saw him when he left for work five days ago. At that time he appeared normal but complained of a headache, and took some ibuprofen.

During the clerking, he is noted to have repetitive chewing movements of the mouth. Again, the assessment is interrupted by a tonic-clonic seizure which does not terminate after 10mg of intravenous diazepam. After 15 minutes he is loaded with phenytoin. He continues to fit so is intubated and transferred to the Intensive Care Unit. Termination of seizure activity is only achieved after induction of general anaesthesia with thiopentone.

What is the most likely diagnosis?

[Schizophrenia7%Fronto-temporal dementia10%Acute intermittent porphyria13%Post-ictal psychosis9%Autoimmune limbic encephalitis61%](#)

Autoimmune limbic encephalitis presents with acute or sub-acute cognitive dysfunction, behavioural changes, and seizures. A number of specific antibody-related syndromes have been described. The description given here is suggestive of anti-NMDA receptor encephalitis, with a prodromal headache followed by prominent psychiatric features, with orofacial dyskinesias, insomnia, and progression to seizures.

Schizophrenia is a common cause of psychosis but the seizures should point away from a psychiatric disorder towards an organic brain pathology.

Fronto-temporal dementia is a slowly progressive condition.

Acute intermittent porphyria may cause a range of neurological manifestation including psychosis and seizures, but there are no features here that point specifically to this diagnosis.

Post-ictal psychosis is a rare manifestation of the post-ictal state, typically in patients who have had epilepsy for some time. The rapid development of psychosis and seizures in a previously well person should prompt the search for an alternative diagnosis.

## Autoimmune encephalitis

Types of autoimmune encephalitis include:

- autoimmune limbic encephalitis (paraneoplastic and non-paraneoplastic)
- Rasmussen's encephalitis
- anti-NMDAR (NR1) encephalitis
- glycine-receptor mediated encephalitis
- Bickerstaff brainstem encephalitis

### Question 6 of 238

A 24-year-old female known epileptic presents via blue-light ambulance with a generalised tonic-clonic seizures in the Emergency Department. She is currently 24 weeks pregnant and her husband reports she has suffered from epilepsy since she was 5 years old. He is extremely distressed and is unclear which anti-epileptics she normally takes. On our arrival, the Emergency Department registrar has already administered two intravenous boluses of lorazepam 4mg. At 10 minutes since the onset of limb jerking, she continues to jerk all four limbs with low amplitude, rhythmic movements with loss of urinary continence. What is the most appropriate course of action?

[Intravenous phenytoin loading36%](#) [Intravenous sodium valproate8%](#) [3rd dose of intravenous lorazepam11%](#) [Intravenous levetiracetam 37%](#) [Observe and monitor8%](#)

The patient has not terminated her seizure after ten minutes and two doses of intravenous benzodiazepines: she is in status epilepticus. Inaction would be dangerous due to the risk of status to mother and foetus. However, intravenous phenytoin and sodium valproate are both inappropriate in the second trimester of pregnancy. Phenytoin is teratogenic and increases the risk of craniofacial abnormalities and mental retardation, sodium valproate is associated with neural tube, skeletal and urogenital abnormalities. Repeated loading of benzodiazepines is dangerous due to accumulation and subsequent possible toxicity. Intravenous levetiracetam is thus the most appropriate choice, at 30mg/kg, administered as an infusion over 10 minutes<sup>1</sup>.

1. Jones S et al. A protocol for the in-hospital emergency drug management of convulsive status epilepticus in adults. Pract Neurol 2014; 14: 194-7

## Status epilepticus

This is a medical emergency. The priority is termination of seizure activity, which if prolonged will lead to irreversible brain damage. First-line drugs are benzodiazepines such as diazepam or lorazepam. If ineffective within 10 minutes it is appropriate to start a second-line agent such as phenytoin, sodium valproate, levetiracetam, or phenobarbital. If no response within 30 minutes from onset, then the best way to achieve rapid control of seizure activity is induction of general anaesthesia.

### Question 7 of 238

A young woman (aged 23) attends the first seizure clinic following a tonic-clonic seizure 10 days previously. She is diagnosed with epilepsy based on clinical history from her boyfriend who witnessed the full seizure. On questioning she is keen to have a family but not in the immediate future.

What is the most appropriate anti-epileptic?

[Sodium valproate22% Phenytoin5% Carbamazepine13% Levetiracetam17% Lamotrigine44%](#)

ALL anti-epileptics have the potential to cause neural-tube defects. It is widely considered that carbamazepine and lamotrigine are the safest to use in pregnancy. The risk of neural-tube defects can be further reduced by planning pregnancy and the use of folic acid.

Both lamotrigine and carbamazepine are considered 'safest' in pregnancy, especially when compared to valproate and phenytoin. In this case of a primary generalised seizure lamotrigine is the most appropriate choice as a first line agent, with carbamazepine being a second line drug in this presentation.

The use of lamotrigine in pregnancy is investigated here -  
<http://www.ncbi.nlm.nih.gov/pubmed/22594849>

The investigation, diagnosis and treatment of epilepsy is shown in this SIGN guideline -  
<http://www.sign.ac.uk/pdf/sign70.pdf>

## Epilepsy: pregnancy and breast feeding

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus. All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy to minimise the risk of neural tube defects. Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

Other points

- aim for monotherapy
- there is no indication to monitor antiepileptic drug levels
- sodium valproate: associated with neural tube defects
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Breast feeding is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn

### **Sodium valproate**

The November 2013 issue of the Drug Safety Update also carried a warning about new evidence showing a significant risk of neurodevelopmental delay in children following maternal use of sodium valproate.

The update concludes that sodium valproate should not be used during pregnancy and in women of childbearing age unless clearly necessary. Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.

### **Question 2 of 231**

A 45 year old previously fit and well man presents to the emergency department with worsening leg weakness. He is in full time employment as a brick layer and is normally very active. Over the last 24 hours he has started dragging his feet and feels unsteady when walking, describing his gait 'like a drunk man'. On questioning he also describes increasing difficulty passing urine and has not had the sensation to empty his bladder for the past eight hours. He denies any preceding trauma, recent viral illness or similar previous symptoms in the past.

On examination he has normal muscle bulk and no fasciculations. There is symmetrical lower limb flaccid paralysis to the hips, with symmetrical hyporeflexia. He has a sensory level to T10 and is in urinary retention. Examination of the upper limbs and cranial nerves is entirely normal. Which of the following would be the most useful initial investigation?

[Aquaporin 4 antibodies9% Lumbar puncture10% MRI spinal cord67% MRI brain8% HIV serology6%](#)

This man presents with signs and symptoms of acute transverse myelitis. The underlying aetiological process can be diverse; it can be associated with underlying autoimmune systemic response, infectious cause or demyelinating process such as neuromyelitis optica.

The presence of a sensory level suggests a spinal cord lesion, as such a CT or MRI Brain would not be the first investigation. The most important initial approach in a patient presenting with acute disturbance of motor, sensory or autonomic function (and a sensory level) is to rule out a compressive cord lesion; an MRI spine is therefore an essential first step. Although HIV serology would be important in this patient, as aforementioned, the most important step is to exclude a compressive lesion.

## **Transverse myelitis**

### **Causes of transverse myelitis**

- viral infections: varicella zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, human immunodeficiency virus
- bacterial infections: syphilis, Lyme disease
- post-infectious (immune mediated)
- first symptom of multiple sclerosis (MS) or neuromyelitis optica (NMO)

### **Question 5 of 231**

A 42-year-old female presented with a 6-month history of weakness affecting her upper limbs. She found that this was worse at the end of the day, particularly if she had been doing a lot of lifting. She also reported occasional difficulty in swallowing at the end of the day, with drinks causing her to cough. She had been prescribed pyridostigmine, but she stopped taking this as she had not noticed any benefit.

On examination, there was a mild partial ptosis, and a slight facial droop bilaterally. Extra-ocular

movements were normal. Power in shoulder abduction was grade 4/5 bilaterally, but was reduced to 3/5 after repeatedly abducting and adducting the shoulder 20 times. Tone and sensation were normal.

Initial investigation results are shown below:

Nerve conduction studies: Decremental response to repetitive nerve stimulation

Single-fibre electromyography: Increased jitter

Anti-Jo antibodies: Negative

Anti-Mi2 antibodies: Negative

Anti-acetylcholine receptor antibodies: Negative

Which of the following immunological tests is most likely to contribute to the diagnosis?

[Anti-muscle-specific tyrosine kinase \(MuSK\) antibodies 60%](#)  
[Anti-N-methyl D-aspartate \(NMDA\) receptor antibodies 8%](#)  
[Anti-glutamic acid decarboxylase \(GAD\) antibodies 6%](#)  
[Anti-acetylcholine receptor antibody 19%](#)  
[Anti-Hu antibodies 6%](#)

This patient presents with weakness affecting the upper limbs, eyelids, facial muscles and pharynx, which demonstrates fatigability. This is a characteristic description of myasthenia gravis, and this is supported by the electrophysiological tests. The majority of patients with this condition are positive for anti-acetylcholine receptor antibodies, which are present in about 85%. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies. In anti-acetylcholine receptor negative cases, response to acetylcholinesterase inhibitors (such as pyridostigmine) tends to be worse.

Anti-aquaporin antibodies are associated with neuromyelitis optica, anti-N-methyl D-aspartate receptor antibodies are associated with autoimmune encephalitis, anti-glutamic acid decarboxylase antibodies are associated with stiff man syndrome, and anti-Hu antibodies are associated with a paraneoplastic sensory neuropathy and encephalitis.

## **Myasthenia gravis**

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle



- ptosis
- dysphagia

### Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

### Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

### Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

### Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

### Question 6 of 231

A 65-year-old man attends neurology clinic for review of his long-standing trigeminal neuralgia. He had first experienced symptoms five years previously and been troubled by his illness ever

since despite frequent neurology review. The patient experiences attacks of severe shooting pain affecting the right side of his lower face, each episode usually lasting about one hour. The interval between attacks has steadily reduced over the years so that at the present time the patient experiences four to five episodes per week. The patient describes that his symptoms are profoundly limiting his life and that he rarely leaves his house for fear of an attack.

Four years previously, treatment with carbamazepine had been introduced with an initially good response to symptoms. However, patient proved to be intolerant of carbamazepine due to drowsiness. Subsequent trials of treatment with oxcarbazepine, lamotrigine and baclofen had not given lasting relief.

The patient had recently been diagnosed with depression and initiated on treatment with sertraline. He was also suffered from type 2 diabetes currently managed with diet and metformin 500 mg TDS. The patient lived with his wife and had been unable to work as a school-teacher for the past two years due to his symptoms.

Having previously been reluctant to consider surgical intervention, the patient now felt he would be willing to try any options that could improve his symptoms.

MRI brain with / without contrast: sinuses unremarkable without evidence of inflammation; no space occupying lesion; no extra-cranial mass along course of trigeminal nerves; no evidence of widespread demyelination plaque; no evidence of previous infarction; no abnormal enhancement of the trigeminal nerves.

What is the appropriate surgical intervention for this patient?

[Stereotactic radiosurgery18% Balloon compression7% Microvascular decompression49% Radiofrequency lesioning14% Glycerol rhizolysis12%](#)

The patient has long-standing and severe trigeminal neuralgia with life-limiting symptoms despite appropriate medical treatment. Surgical intervention should therefore be considered.

In around 95 % of cases, trigeminal neuralgia is believed to be caused by compression of the trigeminal nerve by adjacent blood vessels, although the exact mechanism of the pathophysiology is incompletely understood. In a minority of cases, trigeminal neuralgia can be due to an alternative diagnosis such as sinusitis, extra-cranial or intra-cranial masses, multiple sclerosis or infarction of the thalamus or brainstem.

The MRI brain undergone by the patient does not provide evidence for any of the rare causes of trigeminal neuralgia with the patient's symptoms therefore very likely due to vascular compression. Using specialist techniques not included in the standard protocol, MRI can detect vascular contact with the trigeminal nerve. However, vascular contact with cranial nerves is also a normal variant in some individuals so these techniques are not routinely used.

Microvascular decompression is therefore the surgical technique of choice and is effective treatment in 95 % of such cases of trigeminal neuralgia. The other possible answers refer to methods of palliative destruction of the trigeminal nerve root, therefore carrying the risk of

causing facial numbness. However, they are effective in the minority of trigeminal neuralgia cases not caused by vascular compression.

Zakrzewska J, Linskey M. Trigeminal neuralgia. BMJ 2014;348:g474.

## **Trigeminal neuralgia**

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur

The International Headache Society defines trigeminal neuralgia as:

- a unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
- the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- the pains usually remit for variable periods

## **Management**

- carbamazepine is first-line
- failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

## **Question 7 of 231**

You are seeing a 25-year-old woman in neurology outpatients clinic who has been struggling with her migraines for the past 7 years. She has to use abortive medication five to six times a month and she still has issues with her control, with migraines often lasting half a week. Over the seven years she has tried three different triptans, and combinations of NSAIDs (non-steroidal anti-inflammatory drugs), paracetamol and triptans with limited success. Two years ago she had a trial without medication for three months and her headaches got significantly worse. The only other medication that she takes is the combined oral contraceptive pill.

What would be the next step in achieving migraine control?

[Topiramate22%](#)[Pizotifen9%](#)[Propranolol49%](#)[Acupuncture7%](#)[Re-attempt withdrawal of medication12%](#)

This is a lady who would benefit from preventative medication. The criteria for considering preventative medication is as follows:

- Causing frequent disability - e.g. two to three migraines per month lasting 3 or more days
- At risk of medication overuse headache - (this must be ruled out, and has from previous withdrawal attempt)
- Standard analgesia and triptans contraindicated or ineffective
- Migraine is of uncommon type (this requires specialist advice)

Topiramate and propranolol are both first line preventative medications.

Gabapentin and acupuncture are second line preventative strategies and should be considered if first line treatment fails after two months.

As this lady is of child-bearing age, and has no contraindications, propranolol would likely be the best choice for her. Topiramate is teratogenic and can interfere with the effectiveness of hormonal contraceptives, so less than ideal in this case.

NICE guidelines migraine

<http://cks.nice.org.uk/migraine#!scenario>

## **Migraine: management**

It should be noted that as a general rule 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis. NICE produced guidelines in 2012 on the management of headache, including migraines.

### **Acute treatment**

- first-line: offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol
- for young people aged 12-17 years consider a nasal triptan in preference to an oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide\* or prochlorperazine and consider adding a non-oral NSAID or triptan

## Prophylaxis

- prophylaxis should be given if patients are experiencing 2 or more attacks per month. Modern treatment is effective in about 60% of patients.
- NICE advise either topiramate or propranolol 'according to the person's preference, comorbidities and risk of adverse events'. Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives
- if these measures fail NICE recommend 'a course of up to 10 sessions of acupuncture over 5-8 weeks' or gabapentin
- NICE recommend: 'Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
- for women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- pizotifen is no longer recommend. Adverse effects such as weight gain & drowsiness are common

\*caution should be exercised with young patients as acute dystonic reactions may develop

## Question 8 of 231

You receive a call from a GP in the community. A 65-year-old female patient who was diagnosed with generalised myasthenia gravis six years ago and last reviewed in neurology outpatients 6 weeks ago reports no improvements in her neck weakness, voice weakness and fatigue. In the neurology clinic, her dose of pyridostigmine was increased from 90mg QDS to 120mg QDS. She does not appear acutely unwell but complains that her life is significantly affected by her symptoms. She has no other past medical history. On examination by her GP, she has no respiratory distress and able to swallow salivary secretions normally. What is your advice?

[Increase pyridostigmine to 150mg QDS12%](#)[Start prednisolone 60mg in community, neurology to follow up in 8 weeks as outpatient35%](#)[Start azathioprine in community, neurology to follow up in 8 weeks as outpatient9%](#)[Admit to hospital, start oral prednisolone in hospital30%](#)[Admit to hospital, start intravenous immunoglobulin in hospital15%](#)

The patient remains symptomatic despite being increased onto the maximum dose of pyridostigmine. The second decision is whether the patient is acutely, severely unwell, in which case rapid therapies such as IV Ig or plasmapheresis must be initiated, as per myasthenic crisis. In this case, she has no signs of respiratory distress or dysphagia, her symptoms are more of a case of not improved instead of rapid deterioration. Therefore, the patient does not require rapid

therapy. However, she does require immunotherapy initiation. As a rule of thumb, patients who remain symptomatic despite 60mg QDS of pyridostigmine should be considered for immunotherapy.

The modality of immunotherapy must be individualised to the patient, as each drug has their own contraindications. In younger patients with no concerns regarding blood sugars, oral prednisolone is reasonable. Those with liver disease should avoid azathioprine, renal disease patients should avoid ciclosporin while those with haematological abnormalities should avoid mycophenolate and azathioprine.

However, starting of prednisolone, particularly at high doses, have been classically described to cause a paradoxical reaction in half of all patients, resulting in a transient deterioration before improvements are observed. Up to 10% of patients have been reported to have sufficiently severe respiratory failure requiring mechanical ventilation<sup>1</sup>. Initiation of prednisolone should, therefore, take place in a monitored hospital setting.

1. Miller RG, Milner-Brown HS, Mirka A. Prednisone-induced worsening of neuromuscular function in myasthenia gravis. *Neurology*. 1986;36(5):729.

### **Myasthenia gravis: exacerbating factors**

The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of myasthenia gravis . Symptoms become more marked during the day

The following drugs may exacerbate myasthenia:

- penicillamine
- quinidine, procainamide
- beta-blockers
- lithium
- phenytoin
- antibiotics: gentamicin, macrolides, quinolones, tetracyclines

Question 9 of 231

A 32 year-old accountant presents to the neurology clinic.

For the last year he has been troubled by severe headaches. These occur in the morning, sometimes waking him from sleep. There is a sudden onset of stabbing pain behind the left eye, at the onset of which he feels the need to pace around the room, pounding his head in an effort to ease the pain. During the attacks his left eye is watery and his nose is congested. On more than one occasion he has noticed that his right pupil appears enlarged during the attacks. He tells you very clearly that the pain is so severe that at times during the attacks he has considered jumping out of the top floor of the office building where he works. Each attack lasts one or two hours, and between the attacks he feels fine.

He shows you a detailed headache diary in which he has documented every attack over the last year. For example, in January he had a period of nine days in which attacks occurred several times daily, but in February and March he was headache free. During April he developed severe headaches which occurred almost every day until June. He then had another period of relief until August, and so on.

He has no other past medical history and no allergies.

Examination is unremarkable.

What is the best treatment for prophylaxis of this man's headaches?

[100% oxygen 10% Verapamil 68% Sumatriptan 7% Propranolol 10% Lithium 4%](#)

This is a classic description of episodic cluster headache.

Interestingly, the patient mentioned that his right pupil was enlarged, but most likely he is describing ipsilateral Horner's syndrome, which may occur during cluster attacks.

Verapamil is the established first-line agent for the prophylaxis of episodic and chronic cluster headache.

100% oxygen is the first-line treatment for acute attacks of cluster headache.

Sumatriptan is commonly used for acute attacks of cluster headache and migraine, often subcutaneously.

Propranolol is a first-line drug for the prophylaxis of migraine.

Lithium is a second-line agent for the prophylaxis of cluster headache.

## **Cluster headache**

Cluster headaches are known to be one of the most painful conditions that patients can have the misfortune to suffer. The name relates to the pattern of the headaches - they typically occur in clusters lasting several weeks, with the clusters themselves typically once a year.

Cluster headaches are more common in men (3:1) and smokers. Alcohol may trigger an attack and there also appears to be a relation to nocturnal sleep.

### Features

- pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- clusters typically last 4-12 weeks
- intense sharp, stabbing pain around one eye (recurrent attacks 'always' affect same side)
- patient is restless and agitated during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

### Management

- acute: 100% oxygen (80% response rate within 15 minutes), subcutaneous triptan (75% response rate within 15 minutes)
- prophylaxis: verapamil is the drug of choice. There is also some evidence to support a tapering dose of prednisolone
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

Some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

### Question 10 of 231

A 64 year old man presented to the Emergency Department after becoming unwell at home. His wife reported that the patient experienced a sudden onset and severe headache while watching television. Shortly afterwards she found him to have become confused and drowsy and an ambulance was called. On arrival in the Emergency Department, the patient suffered a witnessed tonic-clonic seizure, self-terminating after two minutes.

The patient had known hypertension and hypercholesterolaemia and had suffered a non-ST



elevation myocardial infarction two years before, treated with a drug-eluting stent to the left anterior descending artery. Regular medications included ramipril 10 mg OD, bisoprolol 10 mg OD, bendroflumethiazide 2.5 mg OD, simvastatin 40 mg OD and aspirin 75 mg OD. The patient's wife reported that compliance with anti-hypertensive medications had been inconsistent and that controlling the patient's blood pressure had been an on-going problem over the previous two years. The patient was a retired builder and ex-smoker.

On examination, the patient was drowsy (GCS M4V2E3) but was protecting his own airway. Pupils were equal and reactive. The patient was spontaneously moving all his limbs and had downgoing plantar reflexes. Cardiovascular, respiratory and abdominal examination was unremarkable. Initial observations and investigations are listed below.

Blood pressure 220 / 115 mmHg  
Heart rate 89 beat / minute  
O2 sats (15 L O2) 100 %  
Respiratory rate 19 / minute  
Temperature 37.1°C.

CT brain: no extra-axial bleeding or collection; no intracerebral haemorrhage; no evidence acute ischaemic stroke; no subarachnoid blood; normal ventricular system; mild small vessel disease in keeping with patient's age.

Lumbar puncture:

CSF red cells 3 / mm<sup>3</sup>  
CSF white cells 3 / mm<sup>3</sup>  
CSF gram stain unremarkable  
CSF glucose 60 % serum level  
protein 0.5 g / L  
CSF negative for bilirubin and xanthochromia

Given persistent reduced GCS and need to obtain blood pressure control, patient was intubated and transferred to the neuro intensive care unit. Following discussion with neurological team further imaging was arranged

MR brain with angiography: structurally normal brain as per previous study; bilateral symmetric vasogenic oedema involving the subcortical white matter in the parietal-occipital, posterior temporal and posterior frontal lobes; MRA unremarkable without any area of stenosis or vasospasm.

What is the correct diagnosis?

[Reversible cerebral vasoconstriction syndrome31%](#)[Posterior reversible leucoencephalopathy syndrome39%](#)[Acute disseminated encephalomyelitis11%](#)[Cerebral venous thrombosis10%](#)[Pituitary apoplexy9%](#)

Posterior reversible leucoencephalopathy syndrome may present with thunderclap headache, usually followed rapidly by confusion, seizures and visual symptoms. CT brain and lumbar puncture results are usually normal or near normal. The most common causes of PRES are hypertensive encephalopathy (as in this case) and eclampsia. Hypertension is commonly observed. Diagnosis is made by evidence of vasogenic brain oedema on MRI brain. PRES is often associated with reversible cerebrovascular vasoconstriction syndrome with vasospasms on angiography (although not in this case). Acute disseminated encephalomyelitis does not present with thunderclap headache.

Cerebral sinus thrombosis and pituitary apoplexy can both present with thunderclap headache and normal CT brain and LP although the other results and clinical picture in this case are not consistent with these diagnoses. Acute disseminated encephalomyelitis does not present with thunderclap headache.

Ducros A, Boussier M. Thunderclap headache. BMJ 2012;345:e8557.

## **Thunderclap headache**

Thunderclap headache describes a sudden (reaches maximum severity within seconds to minutes of onset) and severe headache.

### **Causes**

- subarachnoid hemorrhage
- cerebral venous sinus thrombosis
- internal carotid artery dissection
- pituitary apoplexy
- reversible cerebral vasoconstriction syndrome
- primary sexual headache
- posterior reversible leucoencephalopathy syndrome

### **Question 1 of 220**

A 35-year-old female presents to the Emergency Department with worsening lower limb weakness over a three day period. She is now unable to walk and feels that her fingers are becoming clumsy. On examination her heart rate is 65 beats per minute and regular, her blood

pressure is 125/70 mmHg and her respiratory rate is 20 breaths per minute. She has absent ankle and knee jerks and reduced reflexes in the upper limbs.

Her cerebrospinal fluid (CSF) study shows an elevated protein with a normal white cell count. Given her likely diagnosis, which of the following parameters is most important to measure throughout her admission?

[Lower limb power](#)4%[Serial CSF protein levels](#)4%[Forced expiratory volume over 1st second \(FEV1\)](#)13%[Postural blood pressure](#)4%[Forced vital capacity \(FVC\)](#)74%

The most common cause of death in patients with the severe Guillain-Barre Syndrome (GBS) is respiratory failure. This is due primarily to weakness in chest wall muscles, but may also be due to bulbar dysfunction and aspiration. Patients may require intensive care admission and ventilatory support.

For this reason, it is of great importance that forced vital capacity (FVC) is measured on a routine basis and results documented so that additional support can be sought as soon as possible. FEV1 may be preserved in early deterioration as it is not a measure of vital capacity or a marker of chest wall expansion. Therefore, a reduction in FVC is a more sensitive marker of deterioration.

## **Guillain-Barre syndrome: management**

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*).

### **Management**

- plasma exchange
- IV immunoglobulins (IVIG): as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function

### **Prognosis**

- 20% suffer permanent disability, 5% die

### Question 3 of 220

A 58-year-old female with known myasthenia gravis complains of increasing tiredness and reducing exercise tolerance over the past 3 days. During your examination, she has a weak voice is unable to finish her sentences and appears slightly slumped in the chair she is sitting in. What is the most important investigation at this acute stage?

[Forced vital capacity \(FVC\)66% 12 lead ECG6% Forced expiratory volume in 1 second \(FEV1\)16% Blood tests including full blood count, U+Es, LFTs, CRP7% Chest x-ray6%](#)

The patient is approaching a myasthenic crisis. One of the most acute dangers to be aware of is impending respiratory distress, caused by a failure of respiratory muscles. Other symptoms can include dysphonia, dysphagia and generalised weakness. Forced vital capacity is the most accurate assessment of inspiratory and expiratory mechanisms. FEV1 is better at demonstrating an obstructive than respiratory muscle strength. Although blood tests and chest radiography may be useful in identifying an underlying infective cause for the deterioration, the acute issue remains the patients possible progressive respiratory deterioration, which may warrant elective intubation.

## Myasthenia gravis

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

### Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

## Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

## Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

## Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

## Question 6 of 220

A 60-year-old female presents to the Emergency Department with altered sensation in both hands and reduced visual acuity in the left eye. She states that these symptoms have slowly worsened over a week. She has no issues with bladder or bowel activity.

On examination, she is haemodynamically stable. Of note, she has a sensory loss throughout her arms and legs, but no clear sensory level. Additionally, she has brisk reflexes in both the upper and lower limbs. She also has a visual acuity of 6/36 in the left eye, but normal vision in the right eye, with normal visual fields.

Her MRI scan reveals multiple continuous segments of inflamed spinal cord throughout the cervical region and left optic nerve inflammation. There are no cerebral lesions. Her

cerebrospinal fluid (CSF) studies are negative for oligoclonal bands.

Which of the following tests will confirm the diagnosis?

[dsDNA antibodies6% Aquaporin-4 antibodies65% ACh receptor antibodies6% NMDA receptor antibodies14% Neuronal antibodies8%](#)

The description of a patient with optic neuritis and longitudinal extensive cervical transverse myelitis with a CSF negative for oligoclonal bands is highly suggestive of neuromyelitis optica (NMO). The classic antibody associated with this disease is NMO-IgG or antibodies against aquaporin-4.

The 2006 diagnostic criteria for NMO are as follows:

Transverse myelitis and optic neuritis with at least 2 of the following features:

- MRI brain negative/nondiagnostic for multiple sclerosis
- MRI spinal cord lesion extending over 3 vertebral segments (LETM)
- NMO-IgG/Aquaporin-4 antibody seropositivity

## **Neuromyelitis optica**

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder. Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations<sup>1</sup>. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria<sup>2</sup>:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

1. Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805.
2. Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485.

#### Question 7 of 220

A 23-year-old investment banking intern presents to the urgent care centre complaining of progressive unsteadiness on walking over the past 6 months. He has no past medical history except type 2 diabetes, which is diet controlled, diagnosed one year ago. He has no family history of any diseases. He has been working very long hours for the past 2 years and reports high levels of stress at work, coupled a culture of 'binge-drinking' to team bond after work. Over the past 3 months, he has noticed a lack of articulation with his speech, which he assumed was secondary to alcohol. He estimates he drinks up to 30 units of alcohol a week. On examination, his cardiovascular, respiratory and abdominal systems are unremarkable. His finger-nose test is impaired bilaterally and is unable to tandem walk. He denies any neck stiffness or headache. He has a full range of eye movements. He has absent reflexes in his lower limbs and upgoing plantars bilaterally. Which investigation will provide the definitive diagnosis?

[MRI head with gadolinium contrast29%](#)[CT angiography including posterior vessels10%](#)[Lumbar puncture9%](#)[Serum genetic testing37%](#)[Muscle biopsy14%](#)

The patient describes cerebellar signs of dysarthria, poor coordination and ataxia, in addition to absent ankle jerks and upgoing plantars, presenting at an early age with progressive symptoms. Friedrich's ataxia and other spinocerebellar ataxias must be considered. A diagnosis of type 2 diabetes is odd in such a young patient. However, up to 1/3 of patients with Friedrich's ataxia experience impaired glucose tolerance or diabetes mellitus. These patients often present with cardiomyopathy as well, causing arrhythmias and heart failures.

This patient presents slightly late, most patients have symptoms by childhood. Up to 90% present by 25 years old<sup>1</sup>. It is often assumed that spinocerebellar ataxias, in this case an autosomal recessive one, must be accompanied by a family history. In 40% of Friedrich's ataxia, there is no positive family history at all<sup>1</sup>.

Diagnosis is by serum genetic testing of the GAA trinucleotide repeat. Treatment is limited but involves a multidisciplinary team of neurologists, cardiologists and endocrinologists. There are theories that iron chelation is important in Friedrich's ataxia but these are yet to be proven in large-scale studies<sup>2</sup>.

1. Dürr A, Cossee M, Agid Y et al. Clinical and genetic abnormalities in patients with Friedrich's ataxia. *N Engl J Med.* 1996;335(16):1169

2. Schulz JB, Dehmer T, Schöls L et al. Oxidative stress in patients with Friedreich ataxia. Neurology. 2000;55(11):1719

## **Friedreich's ataxia**

Friedreich's ataxia is the most common of the early-onset hereditary ataxias. It is an autosomal recessive, trinucleotide repeat disorder characterised by a GAA repeat in the X25 gene on chromosome 9 (frataxin). Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in not demonstrating the phenomenon of anticipation.

The typical age of onset is 10-15 years old. Gait ataxia and kyphoscoliosis are the most common presenting features.

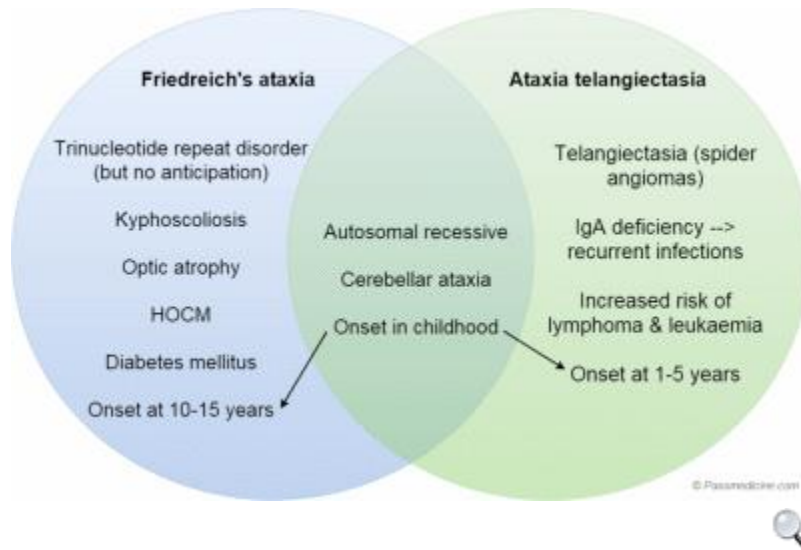
### Neurological features

- absent ankle jerks/extensor plantars
- cerebellar ataxia
- optic atrophy
- spinocerebellar tract degeneration

### Other features

- hypertrophic obstructive cardiomyopathy (90%, most common cause of death)
- diabetes mellitus (10-20%)
- high-arched palate





Comparison of Friedreich's ataxia and ataxic telangiectasia. Note in particular how ataxic telangiectasia tends to present much earlier, often at the age of 1-2 years

#### Question 8 of 220

You review an 80-year old retired teacher in your clinic in your clinic. She has been complaining of numbness on her arms and difficulty walking. On examination you find she has reduced sensation lateral aspect of her arms and forearms in the anatomical position. She has no wasting on the muscles of her hands. She has reduced biceps and supinator reflexes and reduced power bilaterally.

When she gets up to go you notice she has a scissoring gait which is wide based. You ask her to close her eyes and she is unable to stand still without support.

She lives on her own and usually is independent, although recently she has been struggling to cope. She has a background of hypertension and high cholesterol.

What is the most appropriate investigation to diagnose this lady?

[Cervical myelography15%](#)[Cervical X-Ray5%](#)[Nerve conduction studies11%](#)[Nerve biopsy6%](#)[MRI of the cervical cord63%](#)

This lady has lower motor neuron deficit and sensory loss in her upper limbs at the level of C5-C7. She has spastic paraparesis, Romberg +ve indicating loss of proprioception in her lower limbs.

This presentation is suspicious of cervical myelopathy. The main segments which are affected of the cervical cord in this condition are C5-C7, as is the case in this lady. The dermatomal

distribution of her sensory loss is confined to C5-C7 therefore supporting this hypothesis.

Cervical myelopathy is caused by narrowing of the cervical spinal canal, most commonly caused by stenosis. The aetiology includes:

- Cervical cord tumours
- ossification of the posterior longitudinal ligament
- Trauma
- Cervical degenerative changes (spondylosis)
- Cervical degenerative disc disease

The investigation of choice and one which would enable you to assess spinal and foraminal stenosis would be cervical myelography or MRI of the cervical cord. Cervical myelography entails the use of contrast and can be nephrotoxic, whereas MRI is the preferred modality to image and diagnose cervical spondylosis.

### **Peripheral nerves: cervical plexus**

C5,6: deltoid

C5,6: biceps

C5,6,7: serratus anterior (paralysis causes winging of scapula)

Radial

- C5,6: brachioradialis
- C6,7,8: triceps

Median nerve

- C8: finger flexors

Ulnar nerve

### Question 1 of 214

A 25-year-old F1 driver complains of neck pain following a race. Three days later he presents with left sided facial numbness as well as numbness across the right upper and lower limb. Positive findings on examination are the loss of pain and temperature sensation on the left side of the face in all trigeminal distributed areas. There is also the loss of pain and temperature sensation in the right upper and lower limbs. The left pupil is much smaller than the right and there is a partial ptosis on the left. Eye movements are normal. Power, coordination, and reflexes are all normal. What is the gold standard brain-imaging method used in order to establish the primary diagnosis?

[Plain MRI brain](#)12% [Carotid artery doppler ultrasound scan](#)9% [Plain CT scan brain](#)6% [CT angiogram head and neck](#)68% [Electroencephalogram \(EEG\)](#)4%

This gentleman has a vertebral artery dissection following neck hyperflexion during the F1 car race. It is not uncommon for young people to get these sorts of strokes, particularly young sporting people such as in the sad case of the cricketer Phil Hughes.

The vertebral artery has a tributary (the posterior inferior cerebellar artery -PICA) to the medulla and in this case, the F1 driver has therefore developed a left sided lateral medullary syndrome (aka Wallenberg syndrome). Below are the features of this syndrome:

Cerebellar features: ipsilateral limb ataxia, vertigo, nystagmus to the side of the lesion. These are due to taking out the ipsilateral spinocerebellar tracts within the medulla.

Brain stem features:

dizziness and vomiting (taken out the vestibular and vagal nuclei)  
dysphagia and dysarthria (again this represents the vagal nuclei being taken out)  
ipsilateral Horner's syndrome (the sympathetic tract has been taken out on that side)  
ipsilateral facial pain and temperature sensory loss (ipsilateral trigeminal tract taken out)

ipsilateral pharyngeal and laryngeal paralysis from cranial glossopharyngeal and vagus palsies

IMPORTANTLY, contralateral pain and temperature sensory loss (spinothalamic tract taken out. Remember, this crossed over well before the medulla, down at the level of the cord itself).

With all brainstem strokes, the side of the lesion is the side of the cranial nerve sign. Ie...loss of sensation on the left side of the face, for example, but with a loss of sensation of the right side of the body...still tells you that the lesion is on the left because that is the side of the cranial nerve sign. In a left-sided 'ventral pontine syndrome' (Millard Gubler), for example, you get ipsilateral facial weakness (the left facial nerve has gone -ie the cranial nerve sign) with contralateral body hemiparesis (the right corticospinal tract has been taken out).

The management of vertebral artery dissection is actually anticoagulation (once bleed excluded by scans). This is intended to prevent further thromboembolic complications (here, for example,

our patient has had a subsequent brainstem stroke). Note that there are actually no randomised controlled trials to support the use of anticoagulation here, but its what people do. Antiplatelet therapy is a reasonable option to consider in patients who are suspected of suffering from a vertebral artery dissection while awaiting definitive investigations. So here, if a plain CT excluded bleed, then you clearly have a stroke and aspirin would be a reasonable choice whilst you wait for you CT angiogram. Note plain CT would not establish the diagnosis. In order to visualise the dissected vessel, you need an angiogram.

## Stroke by anatomy

Site of the lesion	Associated effects
Anterior cerebral artery	Contralateral hemiparesis and sensory loss, lower extremity > upper
Middle cerebral artery	Contralateral hemiparesis and sensory loss, upper extremity > lower Contralateral homonymous hemianopia Aphasia
Posterior cerebral artery	Contralateral homonymous hemianopia with macular sparing Visual agnosia
Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain)	Ipsilateral CN III palsy Contralateral weakness of upper and lower extremity
Posterior inferior cerebellar artery (lateral medullary syndrome, Wallenberg syndrome)	Ipsilateral: facial pain and temperature loss Contralateral: limb/torso pain and temperature loss Ataxia, nystagmus
Anterior inferior cerebellar artery (lateral pontine syndrome)	Symptoms are similar to Wallenberg's (see above), but: Ipsilateral: facial paralysis and deafness
Retinal/ophthalmic artery	Amaurosis fugax
Basilar artery	'Locked-in' syndrome

## Lacunar strokes

- present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia

- strong association with hypertension
- common sites include the basal ganglia, thalamus and internal capsule

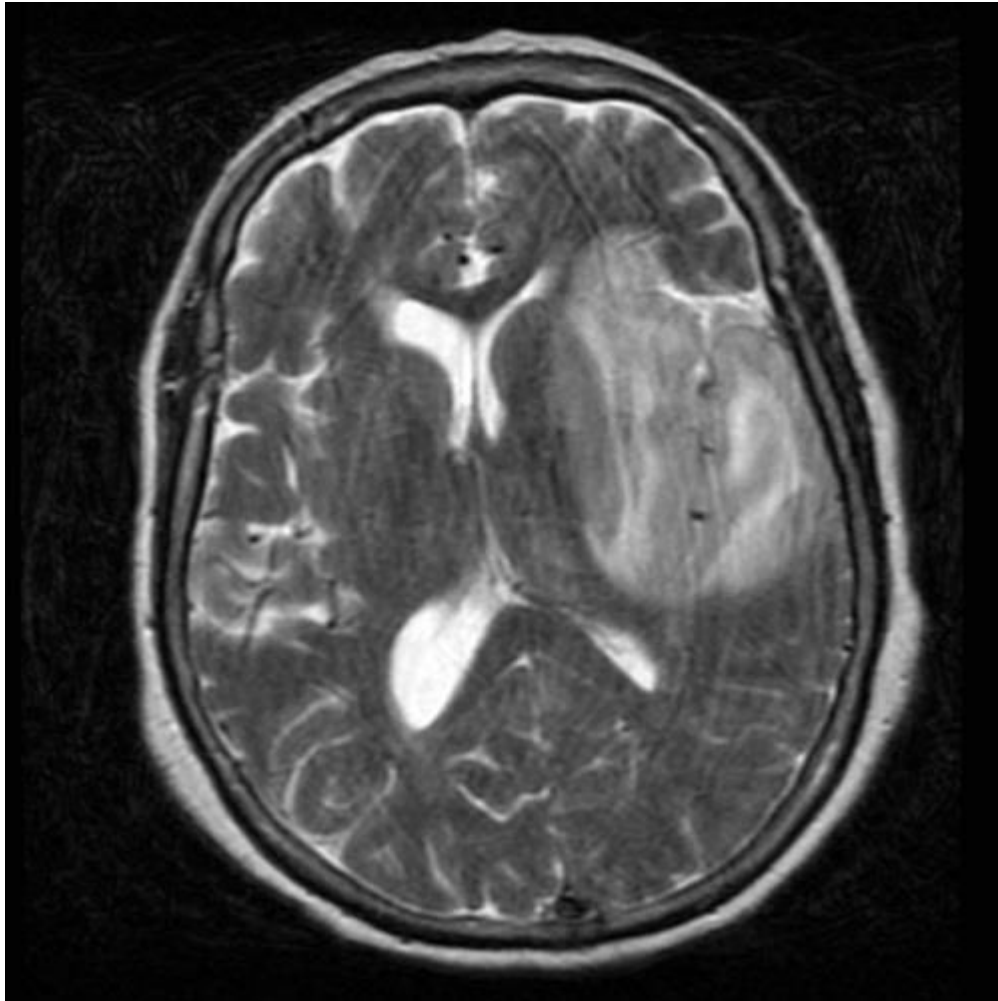
#### Question 5 of 214

A 56-year-old businessman is admitted to the Emergency Department after suffering a seizure. His wife reports that he has been acting 'strange' for the past few days. She has noticed in particular that he has been 'slow' complaining of feeling tired all the time and also having difficulty finding the right words.

One hour after the seizure had terminated the patient remained confused and appeared to have an ataxic gait after getting up from his bed. During the history he repeatedly said the word 'headache'.

On examination his pulse was 84/min, blood pressure 108/74 mmHg, blood sugar 5.2 mmol/l and temperature 37.9°C.

A MRI was requested:



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What is the most likely diagnosis?

[Glioblastoma multiforme](#)26% [Herpes simplex encephalitis](#)48% [Cerebral abscess](#)12% [Cerebral toxoplasmosis](#)6% [Meningioma](#)7%

The MRI shows hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex. These changes are consistent with herpes simplex encephalitis.

Don't be tempted by the 'businessman'/cerebral toxoplasmosis line of thinking - not all businessmen have HIV!

## Herpes simplex encephalitis

Herpes simplex (HSV) encephalitis is a common topic in the exam. The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia

### Features

- fever, headache, psychiatric symptoms, seizures, vomiting
- focal features e.g. aphasia
- peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis

### Pathophysiology

- HSV-1 responsible for 95% of cases in adults
- typically affects temporal and inferior frontal lobes

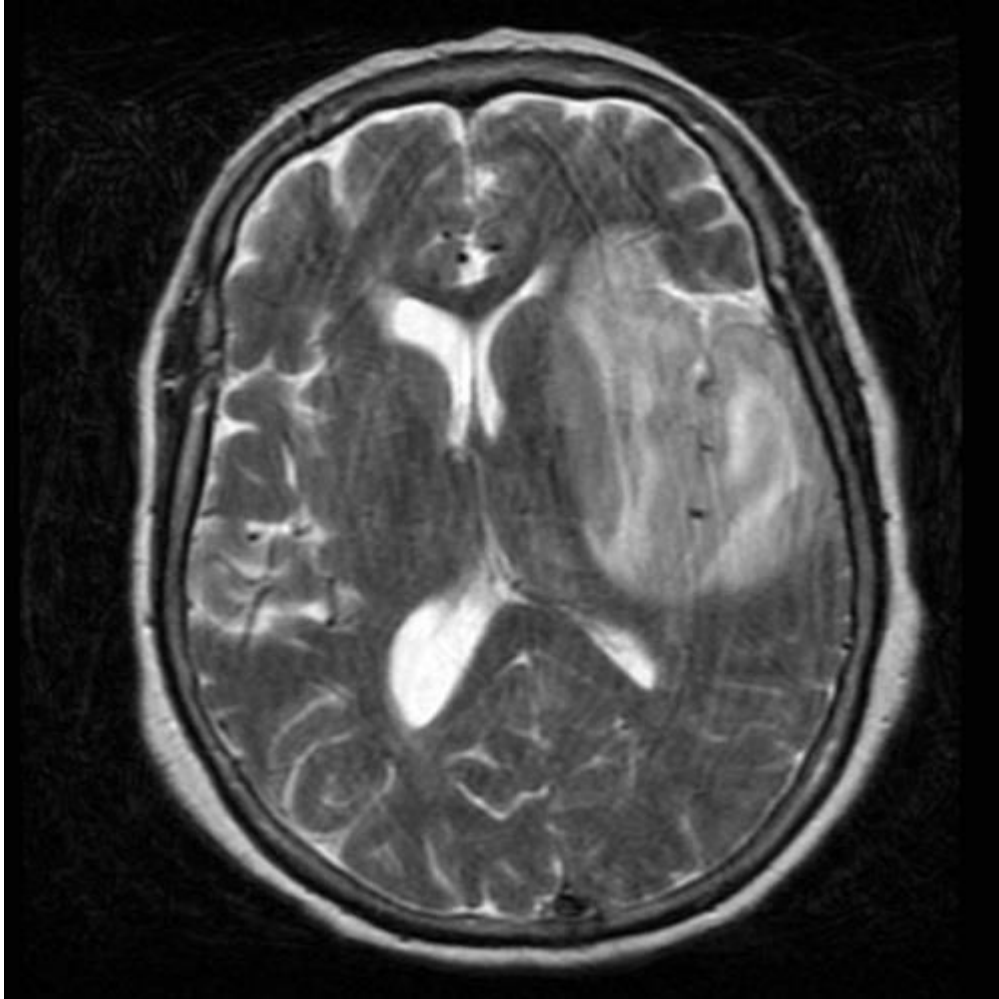
### Investigation

- CSF: lymphocytosis, elevated protein
- PCR for HSV
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) - normal in one-third of patients
- MRI is better
- EEG pattern: lateralised periodic discharges at 2 Hz

### Treatment

- intravenous aciclovir

The prognosis is dependent on whether aciclovir is commenced early. If treatment is started promptly the mortality is 10-20%. Left untreated the mortality approaches 80%



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MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

#### Question 1 of 209

A 58-year-old female is brought into hospital by her husband with recurrent falls associated with cognitive decline noted by her husband over the past 8 weeks. The patient's husband reports a possible cough and cold about 3 months ago, during which she took 2 days off work as a personal assistant to a FTSE 100 company CEO but otherwise has no significant past medical history, is a non-smoker and drinks minimal alcohol.

On examination, she is alert and orientated to time and place but appears easily startled every time you start a sentence. You note significant bilateral finger-nose and heel-shin dysmetria,



mild postural tremor and mild speech slurring. The remainder of her neurological examination was unremarkable.

Her blood tests are as follows:

Hb	124 g/l
Platelets	$282 \times 10^9/l$
WBC	$4.8 \times 10^9/l$
Na <sup>+</sup>	143 mmol/l
K <sup>+</sup>	4.7 mmol/l
Urea	6.7 mmol/l
Creatinine	86 $\mu$ mol/l
CRP	3 mg/l
TSH	8.0 mu/l
Free T4	12.0 pmol/l
Anti-TPO	negative
HIV	negative
Glucose	6.5 mmol/l

A lumbar puncture was performed with results as follows:

WCC	<1 /mm <sup>3</sup>
RBC	28 /mm <sup>3</sup>
Protein	0.71 g/l
Glucose	3.4 mmol/l
Culture	no organisms grown
Viral PCR	awaited
Cytology	awaited
14-3-3	positive

An EEG demonstrated brief periodic spikes but these were not correlated with any seizure activity clinically. An MRI head demonstrated no parenchymal abnormalities except mildly increased signal in the cortical sulci.

What is the most likely diagnosis?

[Creutzfeldt-Jakob disease60%](#)[Viral encephalitis8%](#)[Acute disseminated encephalomyelitis \(ADEM\)12%](#)[Progressive multifocal leucoencephalopathy \(PML\)9%](#)[Hashimoto's encephalopathy10%](#)

This middle aged female demonstrates a number of worrying features suggestive of Creutzfeld

Jakob disease (CJD): rapid cognitive decline, myoclonus, extrapyramidal signs (ataxia), startle response, positive 14-3-3 on CSF and periodic spiking on EEG. The MRI findings likely represent 'cortical ribboning', with high signal on the cortical sulci surfaces, which along with increased signal in putamen and caudate head, is suggestive of CJD.

She is also in the expected age group for CJD, typically presenting between 57 and 62 years old.

A number of features in the history and investigations are red herrings: it is unusual for a viral encephalitis, related to a probable viral respiratory tract infection, to be indolent for 8 weeks and continuing to progress in a non-immunosuppressed patient. The MRI findings and time course are also not suggestive of ADEM, which produces many focal areas of central demyelination within 1 to 3 weeks of a viral illness.

PML results in central demyelinating and is caused by activation of JC papovavirus in immunosuppressed patients, typically HIV positive individuals, and hence unexpected in this patient. The raised TSH likely represents subclinical hypothyroidism in this patient: while Hashimoto's encephalopathy can produce personality change, aggressive and disorientation, myoclonus and ataxia, 14-3-3 is typically negative in CSF with positive anti-TPO antibodies. A diagnosis of CJD is thus most likely diagnosis, with the patient progressing along a typically fatal clinical course.

## **Creutzfeldt-Jakob disease**

Creutzfeldt-Jakob disease (CJD) is rapidly progressive neurological condition caused by prion proteins. These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.

### **Features**

- dementia (rapid onset)
- myoclonus

### **Investigation**

- CSF is usually normal
- EEG: biphasic, high amplitude sharp waves (only in sporadic CJD)
- MRI: hyperintense signals in the basal ganglia and thalamus

### **Sporadic CJD**

- accounts for 85% of cases
- 10-15% of cases are familial
- mean age of onset is 65 years

#### New variant CJD

- younger patients (average age of onset = 25 years)
- psychological symptoms such as anxiety, withdrawal and dysphonia are the most common presenting features
- the 'prion protein' is encoded on chromosome 20 - it's role is not yet understood
- methionine homozygosity at codon 129 of the prion protein is a risk factor for developing CJD - all patients who have so far died have had this
- median survival = 13 months

#### Other prion diseases

- kuru
- fatal familial insomnia
- Gerstmann Straussler-Scheinker disease

#### Question 2 of 209

A 45-year-old female presents with small multiple ischaemic infarcts in the right cerebellar hemisphere confirmed on MRI, associated with small haemorrhages within two areas of infarct. A subsequent CT angiogram 24 hours into the admission demonstrated a right vertebral artery dissection with a free flowing thrombus visualised. What is the optimal management?

[IV heparin infusion38%300mg aspirin 14 days followed by clopidogrel 75mg26%Load with warfarin6%Treatment dose low molecular heparin13%Hold off antiplatelet and anticoagulation17%](#)

It is generally accepted that visualised thrombus requires anticoagulation to prevent it increasing in size and consequent possible embolic showering. However, the patient is still in the hyperacute phase with haemorrhagic transformation within small areas of infarct. The optimal management in this scenario is to offer anticoagulation with the greatest reversibility should intracranial haemorrhage occurs: intravenous heparin is tricky to manage but can be reversed the fastest compared to subcutaneous low molecular weight heparin and warfarin. The patient will require close hourly neurological monitoring and urgent repeat imaging if GCS decreases or new or deteriorating focal neurology presents.

## Stroke: management

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is  $> 3.5$  mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

<b>Absolute</b>	<b>Relative</b>
<ul style="list-style-type: none"><li>- Previous intracranial haemorrhage</li><li>- Seizure at onset of stroke</li><li>- Intracranial neoplasm</li><li>- Suspected subarachnoid haemorrhage</li><li>- Stroke or traumatic brain injury in preceding 3 months</li></ul>	<ul style="list-style-type: none"><li>- Concurrent anticoagulation (INR <math>&gt;1.7</math>)</li><li>- Haemorrhagic diathesis</li><li>- Active diabetic haemorrhagic retinopathy</li><li>- Suspected intracardiac thrombus</li><li>- Major surgery / trauma in preceding 2 weeks</li></ul>

### **Absolute**

- Lumbar puncture in preceding 7 days
- Gastrointestinal haemorrhage in preceding 3 weeks
- Active bleeding
- Pregnancy
- Oesophageal varices
- Uncontrolled hypertension >200/120mmHg

### **Relative**

## **Secondary prevention**

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

A 36-year-old male presents to your outpatient clinic with a progressive history over the past 5 years of increasing, progressive 'clumsiness'. His work colleagues had a long running joke with him that he is poorly coordinated for about the past five years but in recent weeks, he has noticed that he is unable to write legibly or even hold a key still using either hand to open a door. He denies any recent weight loss of night sweats, is otherwise healthy with no other past medical history. He is a lifelong non-smoker with a minimal alcohol history and lives with his wife and 2 children.

On examination, his cranial nerves were unremarkable except for mild multidirectional nystagmus at primary gaze. Fundoscopy was normal. Limb examination revealed a significant impairment of finger-nose and heel-shin testing. His gait, tone, power, sensation and reflexes were normal with downgoing plantars. A brief mini-mental state examination scored 30/30. An MRI head is awaited. His blood tests are as below:

Hb 158 g/l  
Platelets  $323 \times 10^9/l$   
WBC  $6.5 \times 10^9/l$

Na <sup>+</sup>	141 mmol/l
K <sup>+</sup>	4.9 mmol/l
Urea	6.6 mmol/l
Creatinine	85 $\mu$ mol/l
CRP	2 mg/l
Creatine kinase	223 IU/l (50-335)
TSH	3.3 mu/l
Free T4	17 nmol/l
HIV	negative
Anti-neuronal antibodies	negative

Which investigation is most likely to yield the diagnosis?

[Neurogenetics testing45%CT chest, abdomen, pelvis7%Vitamin B12 and folate levels8%Lumbar puncture for cerebrospinal fluid including 14-3-3 and S10022%Anti-GQ1b antibodies17%](#)

There appears to be a chronic onset syndrome of pure ataxia, without systemic features or cognitive impairment, nor history of alcohol excess. The likely diagnosis is one of spinocerebellar ataxias (SCA), in particular one of the classified 'type III' syndrome such as SCA6, an adult onset cerebellar ataxia diagnosed by neurogenetic testing.

It is important to rule out key differential diagnoses however: patients with acute onset cerebellar syndrome should be considered for Miller-Fisher syndrome, a post-viral variant of Guillain Barre syndrome resulting in a triad of ophthalmoplegia, ataxia and areflexia, commonly after gastrointestinal infections, diagnosed with positive anti GQ1b antibodies. The time course for this illness over 5 years makes Miller-Fisher unlikely.

A subacute course of weeks and small number of months should alert you to possible prion disease such as Creutzfeldt-Jakob disease (CJD) and a paraneoplastic syndrome. The former typically presents with rapid cognitive decline and myoclonus, classically with MRI features (pulvinar sign, cortical ribboning), CSF features (14-3-3, S100, real-time QUIC) and EEG features (periodic spiking). The latter can present years before a solid tumour is identified on structural imaging with positive anti-neuronal antibodies, resulting in progressive symptoms as the cerebellum degenerate over months. Due to the low sensitivity of anti-neuronal antibodies, a negative result does not necessarily rule out paraneoplastic syndrome but such a long time course of 5 years would be unusual. The likelihood of identifying a significant mass on cross sectional CT imaging is low.

Lastly, the lack of a alcohol or gastrointestinal history makes cerebellar degeneration due to vitamin deficiency very unlikely. As a result, neurogenetics testing for SCA is most likely to yield the underlying diagnosis.

## **Spinocerebellar ataxia**

Spinocerebellar ataxias are a group of autosomal dominant disorders which are associated with the progressive development of ataxic features such as gait disturbance, nystagmus and tremor. The majority of affected patients develop symptoms within the 3rd and 4th decade.

### **Question 4 of 209**

You are working in a neurology outpatient clinic seeing a patient referred from a local GP clinic. He's a 42-year-old man who has been troubled by severe headaches over the past half a year. These headaches are the worse that he's ever had in his life, describing them as far worse than the compound fracture he sustained three years ago. These headaches tend to happen most nights at around 2am just after he falls asleep. He often paces around his kitchen for a couple of hours and often resorts to bashing his head against the fridge the pain is so bad. When probed further he mentioned that he gets a sense of fullness in his right ear (which is the side that the headache most often occurs on). He remembers having a similar problem a couple of years ago that lasted a few months before resolving on their own.

What medication is most likely to prevent these headaches?

[Oral triptan9%](#) [Home oxygen10%](#) [Pizotifen8%](#) [Propranolol17%](#) [Verapamil56%](#)

NICE guidelines suggest that one should diagnose a cluster headache if:

- Pain lasts 15 minutes to 3 hours and is associated with intense restlessness and agitation.
- Episodes occur with a frequency between one every other day and eight times a day.
- Commonly wakes the person from sleep within 2 hours of going to sleep.
- At least five episode of pain have occurred.
- Headache is associated with at least one autonomic feature occurring on the same side as the pain.

Acute treatment for cluster headaches:

- Subcutaneous or nasal triptan
- High flow oxygen 12L/min - this should be set up at home

Prophylactic treatment:

- Verapamil

<http://cks.nice.org.uk/headache-cluster#!scenario>

## **Cluster headache**

Cluster headaches are known to be one of the most painful conditions that patients can have the misfortune to suffer. The name relates to the pattern of the headaches - they typically occur in clusters lasting several weeks, with the clusters themselves typically once a year.

Cluster headaches are more common in men (3:1) and smokers. Alcohol may trigger an attack and there also appears to be a relation to nocturnal sleep.

Features

- pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- clusters typically last 4-12 weeks
- intense sharp, stabbing pain around one eye (recurrent attacks 'always' affect same side)
- patient is restless and agitated during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority



## Management

- acute: 100% oxygen (80% response rate within 15 minutes), subcutaneous triptan (75% response rate within 15 minutes)
- prophylaxis: verapamil is the drug of choice. There is also some evidence to support a tapering dose of prednisolone
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

Some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

### Question 6 of 209

A 50-year-old man was transferred to a tertiary referral centre with dense right-sided weakness and a Glasgow Coma Score of 8. It was estimated that the onset of this event was 8 hours prior to being found. He had bilaterally up-going plantar responses. He was haemodynamically stable and not known to have any major co-morbidities.

A CT Scan of his brain revealed a moderate area of established infarct within left middle cerebral artery (MCA) territory with massive cerebral oedema and mid-line shift. In this circumstance, which of the following interventions may benefit the patient in the acute period?

[Decompressive hemicraniectomy51%](#) [Intra-arterial clot retrieval9%](#) [Intravenous thrombolysis6%](#) [Intravenous dexamethasone25%](#) [Aspirin through nasogastric tube9%](#)

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.

### Question 7 of 209

A 46-year-old white Caucasian female presents to the Emergency Department after waking up unable to walk and complains about problems with vision in her right eye. The patient says she is normally extremely healthy and the only time she has ever visited her GP was when she had an episode of diarrhoea and vomiting about a week ago. She is understandably distressed as she has

not experienced any symptoms before and has not been previously diagnosed with any medical conditions. She has no drug or family history. Nursing staff report to you that she has been given a pad on her bed as she is incontinent of urine, which she is tearfully embarrassed by.

On examination of her cranial nerves, a right relative afferent papillary defect is noted. Visual acuity and colour vision are 6/6 with 17/17 Ishihara plates on the left, 6/60 with 0/17 Ishihara plates on the right. She reports no diplopia with a full range of eye movements and normal facial sensation. Facial movements are normal. Fundoscopy was unremarkable. Examination of the patient's upper and lower limb power demonstrated normal tone with 2-/5 power on the left arm and leg in all movements; and 4-/5 all movements in right arm and leg. There is a patchy loss of sensation to cotton wool on right lateral wrist and anterior aspect left lateral shin. Both plantars are upgoing. Reflexes are brisk at knee and ankles bilaterally. Anal tone and saddle sensation are intact. The patient's cognitive state is normal on superficial examination.

An urgent MRI head and whole spine demonstrates abnormal high signal in the cervical cord from C3 to C7. Her blood tests were mislabelled and hence unavailable. A lumbar puncture was performed with the following results:

WCC	12 mm <sup>3</sup>
RBC	<1 mm <sup>3</sup>
Protein	0.9 g/l
Glucose	5.2 mmol/l (10.2 mmol/l serum)
Oligoclonal bands	awaited
Viral PCR	awaited

What is the most likely diagnosis?

[Idiopathic intracranial hypertension5% Transverse myelitis17% Miller-Fisher syndrome19% Multiple sclerosis13% Devic's disease46%](#)

A first episode of an optic neuritis and myelitis occurring together is suggestive of a central neuroinflammatory cause. A full range of eye movements makes Miller-Fisher syndrome unlikely (and any ataxia demonstrated is likely secondary to limb weakness). Although there is the temptation of diagnosing multiple sclerosis in a patient with features disseminated in place, the keys to the answer are the sites of the lesion (optic nerve and cervical cord) and the long length of cord involvement beyond 3 vertebral levels, much more suggestive of neuromyelitis optic or Devic's disease. The diagnosis would be clinched by a positive aquaporin 4 antibody.

## **Neuromyelitis optica**

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder. Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations<sup>1</sup>. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria<sup>2</sup>:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

1. Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805.

2. Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485.

#### Question 8 of 209

A 62-year-old woman comes to the gastroenterology clinic for review. She has a history of watery diarrhoea over the course of the past 6 months, where she is opening her bowels some 4-6 times per day. There is other past medical history of hypertension, ischaemic heart disease, Type 2 diabetes and depression.

#### Investigations

Hb	11.5 g/l	Na <sup>+</sup>	139 mmol/l	Bilirubin	12 µmol/l
Platelets	207 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.9 mmol/l	ALP	95 u/l
WBC	8.9 * 10 <sup>9</sup> /l	Urea	7.2 mmol/l	ALT	23 u/l
Neuts	5.6 * 10 <sup>9</sup> /l	Creatinine	100 µmol/l	γGT	56 u/l
Lymphs	1.8 * 10 <sup>9</sup> /l			Albumin	38 g/l
Eosin	0.5 * 10 <sup>9</sup> /l				

Colonoscopy: Mild mucosal oedema only, biopsy reveals lymphocytic infiltration

Which of the following agents is most likely to be the cause of her colonoscopy findings?

[Amlodipine6%](#) [Atorvastatin4%](#) [Lisinopril8%](#) [Metformin41%](#) [Sertraline41%](#)

Sertraline is recognised as highly likely to be associated with lymphocytic colitis, (microscopic colitis associated with lymphocytic infiltration). This conclusion results from a mix of association / epidemiology studies, and case series where removal and re-introduction of medication has been correlated with symptoms and changes in biopsy appearance.

Ref: Münch A, Aust D, Bohr J, et al. Microscopic colitis: Current status, present and future challenges: statements of the European Microscopic Colitis Group. J Crohns Colitis 2012; 6:932

Calcium channel antagonists are not thought to be associated with microscopic colitis, but are uncommonly reported as leading to change in bowel habit including diarrhoea. Metformin leads to bile salt malabsorption which may result in diarrhoea. Statins may be associated with microscopic colitis, although withdrawal and re-challenge evidence is less strong than for sertraline. ACE inhibitors are not known to be associated with microscopic colitis. Diarrhoea was a commonly reported adverse event in lisinopril clinical trials, but this is not thought to be due to microscopic colitis.

### **Selective serotonin reuptake inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.

- citalopram (although see below re: QT interval) and fluoxetine are currently the preferred SSRIs
- sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

### **Adverse effects**

- gastrointestinal symptoms are the most common side-effect
- there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- patients should be counselled to be vigilant for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions

### **Citalopram and the QT interval**

- the Medicines and Healthcare products Regulatory Agency (MHRA) released a warning on the use of citalopram in 2011
- it advised that citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

### Interactions

- NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine
- aspirin: see above
- triptans: avoid SSRIs

Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks. For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week. If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine). Paroxetine has a higher incidence of discontinuation symptoms.

### Discontinuation symptoms

- increased mood change
- restlessness
- difficulty sleeping
- unsteadiness
- sweating
- gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- paraesthesia

A 21-year-old man is referred to the ophthalmology clinic. He has a past medical history of type 1 diabetes mellitus which has been poorly controlled as he has recently started university and is living away from home for the first time. This has caused him to monitor his blood sugars less frequently as he is embarrassed about his medical problem and is keen to fit in. He has no visual symptoms but fundoscopy demonstrates microaneurysms and cotton wool spots. He has no other known medical problems and uses biphasic insulin. His observations are all within normal range visual acuity is normal.

Apart from advising and support in managing his diabetes, how should he be managed?

[Referral for retinal laser treatment24% Annual digital retinal photography32% Six monthly digital retinal photography27% Start ramipril13% Start amlodipine4%](#)

The correct answer is annual digital retinal photography. This patient has developed pre-proliferative diabetic retinopathy and strict diabetic control is important. Apart from that, regular retinal photography can help find proliferative retinopathy in which case laser treatment will be needed. There is no evidence of hypertensive changes.

Diabetic retinopathy in type 1 diabetes

People with type 1 diabetes are at high risk of diabetic retinopathy. On diagnosis, they should be referred to screening services and from that point either undergo annual review or be referred to an ophthalmologist. If signs of proliferative retinopathy occur then the patient should be referred for retinal laser treatment.

Source:

'Type 1 Diabetes in Adults: Diagnosis and Management.' NICE Guideline [NG17]. National Institute of Care and Health Excellence, July 2016

## **Diabetic retinopathy**

Diabetic retinopathy is the most common cause of blindness in adults aged 35-65 years-old. Hyperglycaemia is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes

Endothelial dysfunction leads to increased vascular permeability which causes the characteristic exudates seen on fundoscopy. Pericyte dysfunction predisposes to the formation of microaneurysms. Neovascularization is thought to be caused by the production of growth factors in response to retinal ischaemia

In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy. Recently a new classification system has been proposed,

dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

Traditional classification	New classification
	Mild NPDR
Background retinopathy	<ul style="list-style-type: none"> <li>1 or more microaneurysm</li> </ul>
<ul style="list-style-type: none"> <li>microaneurysms (dots)</li> <li>blot haemorrhages (<math>\leq 3</math>)</li> <li>hard exudates</li> </ul>	Moderate NPDR
Pre-proliferative retinopathy	<ul style="list-style-type: none"> <li>microaneurysms</li> <li>blot haemorrhages</li> <li>hard exudates</li> <li>cotton wool spots, venous beading/looping and intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR</li> </ul>
<ul style="list-style-type: none"> <li>cotton wool spots (soft exudates; ischaemic nerve fibres)</li> <li>&gt; 3 blot haemorrhages</li> <li>venous beading/looping</li> <li>deep/dark cluster haemorrhages</li> <li>more common in Type I DM, treat with laser photocoagulation</li> </ul>	Severe NPDR
	<ul style="list-style-type: none"> <li>blot haemorrhages and microaneurysms in 4 quadrants</li> <li>venous beading in at least 2 quadrants</li> <li>IRMA in at least 1 quadrant</li> </ul>
Proliferative retinopathy	
<ul style="list-style-type: none"> <li>retinal neovascularisation - may lead to vitreous haemorrhage</li> <li>fibrous tissue forming anterior to retinal disc</li> <li>more common in Type I DM, 50% blind in 5 years</li> </ul>	
Maculopathy	
<ul style="list-style-type: none"> <li>based on location rather than severity, anything is potentially serious</li> <li>hard exudates and other 'background' changes on macula</li> <li>check visual acuity</li> <li>more common in Type II DM</li> </ul>	

### Question 1 of 200

A 72-year-old admitted to hospital with VF arrest. The ambulance crew reported an out-of-hospital downtime for 3 minutes before CPR was commenced. In A&E resus, CPR was successful and the patient was intubated after the return of spontaneous circulation. 3 days later, on extubation, the ITU consultant notes confusion and bilateral upper limb weakness, confirmed to be new with a collateral history. A CT head, followed by MRI head, demonstrates bilateral small areas of ischaemic change in bilateral posterior parietal lobes, between middle and posterior cerebral artery territories. CT angiography demonstrates 45% RICA stenosis, 60% LICA stenosis. The cardiac monitor demonstrates atrial fibrillation and echocardiogram demonstrates septal akinesia, consistent with recent MI. What is the likely cause of this patient's stroke?

[Cardiac mural thrombus20%](#)[Left carotid artery stenosis4%](#)[Right carotid artery stenosis3%](#)[Hypotension during cardiac arrest47%](#)[Cardioembolic disease26%](#)

The neuroimaging describes a posterior watershed infarct, in which the areas of ischaemia lie in the most vulnerable regions of the brain in between two cerebral artery territories. Embolic disease and cardiac thrombi can produce bilateral symptoms. However, the specific areas involved suggest regions most prone to ischaemia during the period of systemic hypoperfusion. The two broad categories of differentials to consider include cardiac pump failure and hypovolaemia. In this case, hypoperfusion due to cardiac arrest is most likely.

### Hypoperfusion strokes

Hypoperfusion tends to cause brain injuries at 'watershed' areas that are border zones between the major cerebral arteries.

### Question 2 of 200

An 80-year-old lady is seen in the Emergency Department following a fall at home. She states she tripped over a rug whilst carrying her tea into the living room. She did not hit her head or lose consciousness. She fell onto her right hip and was unable to get up due to pain. She was found by her daughter two hours later.

She has a past history of high blood pressure (for which she takes amlodipine and ramipril) and osteoarthritis. She lives alone and is independent aside from her daughter bringing her shopping. She walks with a stick out of doors.



On examination she is alert and oriented. She has a large bruise over her right hip and a small skin tear on her right arm. Her heart rate is 96 beats per minute and her blood pressure is 110/56 mmHg. Systems examination is normal.

X-rays of her hips and pelvis show osteoarthritic change but no fractures.

She is unable to mobilise with the physiotherapist in the emergency department and is admitted to the ward overnight.

In the early hours of the following morning, she becomes confused and agitated. She is shouting that burglars are trying to steal her belongings. She is not oriented in place or time.

Which tool should be used to assess this lady's mental state?

[4AT](#)14% [Abbreviated Mental Test Score \(AMTS\)](#)23% [Confusion Assessment Method \(CAM\)](#)46% [Mini Mental State Examination \(MMSE\)](#)11% [Montreal Cognitive Assessment \(MoCA\)](#)5%

This lady has multiple risk factors that may have precipitated her delirium. These include:

- Pain
- Possible new opiate use to control pain
- Possible dehydration due to a long lie following a fall
- Rapid change to environment
- Immobility

NICE guidelines currently recommend that delirium is scored and monitored using the Confusion Assessment Method (CAM). If patients are in intensive care, the CAM-ICU should be used.

Delirium is best treated by treating the underlying causes. Should this lady become agitated to the degree where she is a danger to herself, a small dose of haloperidol may be considered.

AMTS, MMSE and MoCA are screening and monitoring tests for cognitive impairment. 4AT is a rapid screening tool for delirium but is not yet recommended in preference to CAM.

Reference: National Institute for Health and Clinical Excellence. Delirium: prevention, diagnosis and management

NICE guidelines [CG103]. 2010.

## Delirium vs. dementia

### Factors favouring delirium over dementia

- impairment of consciousness
- fluctuation of symptoms: worse at night, periods of normality
- abnormal perception (e.g. illusions and hallucinations)
- agitation, fear
- delusions

### Question 3 of 200

A 52-year-old man is admitted to the stroke unit with a right total anterior circulation syndrome (TACS) infarct. He arrived at hospital 2.5 hours after the onset of his symptoms and was treated with intravenous alteplase at 3 hours post-onset.

He is known have an atrial septal defect which was discovered after a murmur was heard at a routine insurance medical several years ago. He works in the oil business and has recently returned from a business trip to Saudi Arabia.

On examination the following day there subtle signs of improvement with increased movement in his left hand. However, the rest of his arm remains flaccid and he has persisting dense hemiplegia affecting his right leg. He has a notable homonymous hemianopia on examination. A routine CT Brain 24-hours post-thrombolysis revealed established ischaemic changes in the MCA territory with new petechial haemorrhage along the border of the infarct.

Later that evening, his conscious level falls. His Glasgow Coma Scale changes from E4 M6 V2, to E2, M4 V2. His blood pressure is 187/112 mmHg.

Urgent bloods reveal:

Haemoglobin	120 g/l
Prothrombin time	27 seconds
Activated partial thromboplastin time (APTT)	49 seconds

What intervention is likely to have the most benefit?

[Correction of coagulopathy 12%](#)[Decompressive craniotomy 47%](#)[Control of blood pressure 26%](#)[Protamine sulphate 8%](#)[Tranexamic acid 7%](#)

This patient is at high risk of malignant middle cerebral artery (MCA) syndrome. Malignant

MCA syndrome typically occurs in younger patients who have suffered an extensive ischaemic stroke (usually in the MCA territory). After infarction the brain swells. As younger brains are likely to have less atrophy, there is less room for expansion. Subsequently, intracranial hypertension develops. This typically presents 48 hours after onset of stroke with reduced conscious level.

Thrombolysis should reduce the risk of infarction and subsequent brain oedema, however, re-canalisation is not achieved in every patient and thus thrombolysed patients can still develop malignant MCA syndrome. Furthermore, this patient was thrombolysed 3 hours after onset and so is likely to have established tissue infarction regardless. Treatment with urgent decompressive craniotomy can be life-saving. The procedure is particularly indicated in situations like this, where the patient has a non-dominant stroke and is, therefore, likely to recover language functions and have a more favourable outcome if they survive the acute event.

Acute haemorrhagic transformation is the main differential in this case. While the change in his conscious level should prompt repeat imaging (which would discriminate bleeding from oedema) the risk of large haemorrhagic transformation >24 hours post-thrombolysis is lower than the risk of malignant MCA syndrome. This is especially true when the previous scan has shown only grade I Haemorrhagic infarction (HI-1) as classified using the ECAS II grading system. Urgent discussion with neurosurgery is recommended.

## **Stroke: management**

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is > 3.5 mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

Absolute	Relative
<ul style="list-style-type: none"><li>- Previous intracranial haemorrhage</li><li>- Seizure at onset of stroke</li><li>- Intracranial neoplasm</li><li>- Suspected subarachnoid haemorrhage</li><li>- Stroke or traumatic brain injury in preceding 3 months</li><li>- Lumbar puncture in preceding 7 days</li><li>- Gastrointestinal haemorrhage in preceding 3 weeks</li><li>- Active bleeding</li><li>- Pregnancy</li><li>- Oesophageal varices</li><li>- Uncontrolled hypertension &gt;200/120mmHg</li></ul>	<ul style="list-style-type: none"><li>- Concurrent anticoagulation (INR &gt;1.7)</li><li>- Haemorrhagic diathesis</li><li>- Active diabetic haemorrhagic retinopathy</li><li>- Suspected intracardiac thrombus</li><li>- Major surgery / trauma in preceding 2 weeks</li></ul>

## Secondary prevention

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
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With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

#### Question 5 of 200

A 48-year-old lady develops a sudden-onset left-sided headache in the face and neck areas 36 hours ago whilst at rest. It is of 10/10 severity and reached this maximum intensity within seconds. It has not subsided since and is throbbing in nature. She also developed a transient period of loss of vision in the left eye lasting 2 hours before resolving. She also says that 'food tastes funny' since these problems developed. On examination, she has small, sluggishly light-responsive left pupil compared to the right and partial left ptosis. The face is otherwise unremarkable to examine as is the remaining neurological examination. Routine blood investigations are unremarkable. Plain computerised tomography (CT) of the head is unremarkable. Lumbar puncture is negative for xanthochromia. CT angiogram of the head and neck vessels demonstrates a pseudo-lumen of the carotid artery. Which of the following treatments would you initiate?

[High flow 100% oxygen15%Prednisolone15%Indomethacin21%Aspirin38%Acetazolamide10%](#)

She has an internal carotid artery dissection on the left side culminating in a partial left-sided Horner's syndrome. The term 'partial' Horner's is used because anhidrosis is absent. The sympathetic fibres innervating the facial sweat glands are anatomically located on the external rather than the internal carotid artery; thus, anhidrosis is not a finding in the setting of internal carotid dissection.

In terms of management, there is little role for surgery in spontaneous carotid artery dissections. All dissections put people at risk of thromboembolic complications because of turbulent flow at the sight, therefore we normally initiate antiplatelet or anticoagulation therapy. There is little evidence for which is better over the other in this area although pragmatically speaking antiplatelets are safer. Candidates for angioplasty and stent placement include patients with persistent ischaemic symptoms despite adequate anticoagulation, patients with a contraindication to anticoagulant/antiplatelet therapy, and patients with significantly compromised cerebral blood flow.

In this particular case, the loss of vision points towards possible amaurosis fugax, backing up the need for anti-thromboembolic agents.

## Horner's syndrome

### Features

- miosis (small pupil)
- ptosis
- enophthalmos\* (sunken eye)
- anhidrosis (loss of sweating one side)

### Distinguishing between causes

- heterochromia (difference in iris colour) is seen in congenital Horner's
- anhidrosis: see below

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhidrosis of the face, arm and trunk	Anhidrosis of the face	No anhidrosis
Stroke	Pancoast's tumour	Carotid artery dissection
Syringomyelia	Thyroidectomy	Carotid aneurysm
Multiple sclerosis	Trauma	Cavernous sinus thrombosis
Tumour	Cervical rib	Cluster headache
Encephalitis		

\*in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos

### Question 1 of 195

A 74-year-old patient with known Parkinson's disease presents for review in the geriatric clinic. He has been suffering from sudden onsets of attacks where he is barely able to move. This has been a problem for the last few months. His symptoms are normally well controlled and attacks occur suddenly, lasting for 30 minutes and then resolving without any intervention. He takes levodopa and carbidopa for his Parkinson's disease which has been on a stable dose for the last three years. On examination, he has a mild unilateral tremor and slight bradykinesia which is worse on the right side. His eye movements are normal and he has no postural symptoms when standing. What is the likely explanation of his symptoms?

[Dyskinesia](#)9% [Vascular Parkinsonism](#)7% [Multi-system atrophy](#)6% [Progressive supranuclear palsy](#)6% [On-off effect](#)73%

The correct answer is on-off effect. Over time, levodopa becomes less effective. Patients can experience after a few years of treatment that their symptoms are well-controlled parts of the day and other times their mobility is heavily affected. This is the most likely explanation given the fact that these symptoms started over two years after treatment and the medication regime will need to be adjusted. A Parkinson-plus syndrome is unlikely as these would not have originally responded to levodopa, and would be associated with other features. For example, progressive supranuclear palsy is associated with gaze palsy whilst multi-system atrophy is associated with postural hypotension. Dyskinesia is continuous writhing movements which occur as a side effect of levodopa.

## Parkinson's disease: management

NICE published guidelines in 2017 regarding the management of Parkinson's disease.

For first-line treatment:

- if the motor symptoms are affecting the patient's quality of life: levodopa
- if the motor symptoms are not affecting the patient's quality of life: dopamine agonist (non-ergot derived), levodopa or monoamine oxidase B (MAO-B) inhibitor

Whilst all drugs used to treat Parkinson's can cause a wide variety of side-effects NICE produced tables to help with decision making:

	Levodopa	Dopamine agonists	MAO-B inhibitors
<b>Motor symptoms</b>	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
<b>Activities of daily living</b>	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
<b>Motor complications</b>	More motor complications	Fewer motor complications	Fewer motor complications
<b>Adverse events</b>	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

\* excessive sleepiness, hallucinations and impulse control disorders

If a patient continues to have symptoms despite optimal levodopa treatment or has developed dyskinesia then NICE recommend the addition of a dopamine agonist, MAO-B inhibitor or catechol-O-methyl transferase (COMT) inhibitor as an adjunct. Again, NICE summarise the main points in terms of decision making:

	<b>Dopamine agonists</b>	<b>MAO-B inhibitors</b>	<b>COMT inhibitors</b>	<b>Amantadine</b>
<b>Motor symptoms</b>	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
<b>Activities of daily living</b>	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
<b>Off time</b>	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
<b>Adverse events</b>	Intermediate risk of adverse events	Fewer adverse events	More adverse events	No studies reporting this outcome
<b>Hallucinations</b>	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this outcome

### **Specific points regarding Parkinson's medication**

NICE reminds us of the risk of acute akinesia or neuroleptic malignant syndrome if medication is not taken/absorbed (for example due to gastroenteritis) and advise against giving patients a 'drug holiday' for the same reason.

Impulse control disorders have become a significant issue in recent years. These can occur with any dopaminergic therapy but are more common with:

- dopamine agonist therapy
- a history of previous impulsive behaviours
- a history of alcohol consumption and/or smoking

If excessive daytime sleepiness develops then patients should not drive. Medication should be adjusted to control symptoms. Modafinil can be considered if alternative strategies fail.



If orthostatic hypotension develops then a medication review looking at potential causes should be done. If symptoms persist then midodrine (acts on peripheral alpha-adrenergic receptors to increase arterial resistance) can be considered.

### **Further information regarding specific anti-Parkinson's medication**

#### Levodopa

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- unwanted effects: dyskinesia (involuntary writhing movements), 'on-off' effect, dry mouth, anorexia, palpitations, postural hypotension, psychosis, drowsiness
- no use in neuroleptic induced parkinsonism

#### Dopamine receptor agonists

- e.g. Bromocriptine, ropinirole, cabergoline, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
- patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence
- more likely than levodopa to cause hallucinations in older patients. Nasal congestion and postural hypotension are also seen in some patients

#### MAO-B (Monoamine Oxidase-B) inhibitors

- e.g. Selegiline
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

#### Amantadine

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
- side-effects include ataxia, slurred speech, confusion, dizziness and livedo reticularis

#### COMT (Catechol-O-Methyl Transferase) inhibitors

- e.g. Entacapone, tolcapone

- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
- used in conjunction with levodopa in patients with established PD

### Antimuscarinics

- block cholinergic receptors
- now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g. procyclidine, benzotropine, trihexyphenidyl (benzhexol)

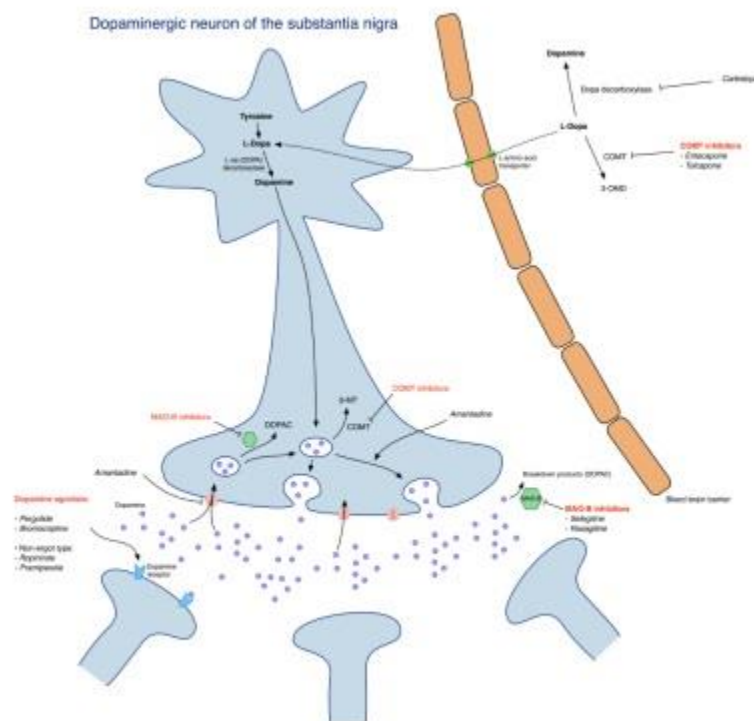


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/File:Dopamine_synthesis_and_metabolism.png)



Diagram showing the mechanism of action of Parkinson's drugs

A 63-year-old man presents to the emergency department with a 5-minute episode of slurred speech earlier in the day. His wife noticed that his face was drooping to one side as well. He had no arm weakness and is now completely back to normal. He is normally well and on no regular medication and is not allergic to any medication. He works as a plumber and smokes 10 cigarettes per day for the last 40 years and drinks alcohol socially. On further questioning he mentions that he had a similar episode also lasting 5 minutes four days ago whilst at work. On examination, his blood pressure is 135/70 mmHg and his heart rate is 58/min. He has no focal neurology and his cardiovascular and respiratory examinations are unremarkable. He has been given 300mg of Aspirin by the paramedics.

His blood tests are as follows:

Hb 138 g/l  
Platelets  $283 \times 10^9/l$   
WBC  $8.1 \times 10^9/l$   
INR 1.1  
PT 13 seconds

Na<sup>+</sup> 142 mmol/l  
K<sup>+</sup> 4.4 mmol/l  
Urea 6.4 mmol/l  
Creatinine 89  $\mu$ mol/l  
CRP 5 mg/l  
Total cholesterol 3.8 mmol/l  
HDL 1.3 mmol/l

His ECG shows normal sinus rhythm and rate of 65/min.

What is the most appropriate management for this patient?

[Outpatient TIA clinic appointment17%](#)[Outpatient CT head and carotid dopplers within the next week22%](#)[Admit for urgent \(< 24 hours\) CT head & carotid dopplers53%](#)[Thrombolysis3%](#)[Long term clopidogrel5%](#)

This gentleman has had crescendo TIAs (2 in a 7 day period). This necessitates treatment as high risk i.e. admission and urgent (<24 hours) CT head and carotid dopplers. His ABCD score is 3 (1 for age and 2 for symptoms). This would normally put him in the low-risk category (see below) but the presence of crescendo episodes the ABCD score is irrelevant. Thrombolysis is not appropriate as the neurology has resolved. OP TIA clinic and imaging and dopplers within the week are not appropriate given the crescendo episodes.

## Transient ischaemic attack

NICE issued updated guidelines relating to stroke and transient ischaemic attack (TIA) in 2008. They advocated the use of the ABCD2 prognostic score for risk stratifying patients who've had a suspected TIA:

Criteria	Points
<b>A</b> Age $\geq$ 60 years	1
<b>B</b> Blood pressure $\geq$ 140/90 mmHg	1
Clinical features	
<b>C</b> - Unilateral weakness	2
- Speech disturbance, no weakness	1
Duration of symptoms	
<b>D</b> - $>$ 60 minutes	2
- 10-59 minutes	1
Patient has diabetes	1

This gives a total score ranging from 0 to 7. People who have had a suspected TIA who are at a higher risk of stroke (that is, with an ABCD2 score of 4 or above) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment and investigation within 24 hours of onset of symptoms
- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors

If the ABCD2 risk score is 3 or below:

- specialist assessment within 1 week of symptom onset, including decision on brain imaging
- if vascular territory or pathology is uncertain, refer for brain imaging

People with crescendo TIAs (two or more episodes in a week) should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.

### Antithrombotic therapy

- clopidogrel is recommended first-line (as for patients who've had a stroke)
- aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel

- these recommendations follow the 2012 Royal College of Physicians National clinical guideline for stroke. Please see the link for more details (section 5.5)
- these guidelines may change following the CHANCE study (NEJM 2013;369:11). This study looked at giving high-risk TIA patients aspirin + clopidogrel for the first 90 days compared to aspirin alone. 11.7% of aspirin only patients had a stroke over 90 days compared to 8.2% of dual antiplatelet patients

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\* criteria or > 50% according to NASCET\*\* criteria

\*European Carotid Surgery Trialists' Collaborative Group

\*\*North American Symptomatic Carotid Endarterectomy Trial

#### Question 4 of 195

A 27-year-old woman comes for review. She is having problems with increasingly frequent migraine attacks. These occur throughout her menstrual cycle and have no relation to her periods. She has tried a combination of paracetamol and ibuprofen to try and control the attacks but this seems to have had a limited effect. Her current medication includes paracetamol and ibuprofen as required and Cerazette (a progestogen-only pill).

What is the most appropriate medication to try and reduce the frequency of her migraine attacks?

[Propranolol62%](#)[Zolmitriptan15%](#)[Topiramate11%](#)[Amitriptyline4%](#)[Switch Cerazette to a combined oral contraceptive pill8%](#)

Propranolol is preferable to topiramate in women of childbearing age (i.e. the majority of women with migraine)

Zolmitriptan is useful to abort attacks but is not generally used for prophylaxis, except in the case of menstrual-related migraine (see below for more details). From the history it is clear that the headaches are not confined to the days around menstruation.

NICE recommend either propranolol or topiramate for migraine prophylaxis. Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives

The combined oral contraceptive pill is contraindicated given her history of migraine.

## **Migraine: management**

It should be noted that as a general rule 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis. NICE produced guidelines in 2012 on the management of headache, including migraines.

### Acute treatment

- first-line: offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol
- for young people aged 12-17 years consider a nasal triptan in preference to an oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide\* or prochlorperazine and consider adding a non-oral NSAID or triptan

### Prophylaxis

- prophylaxis should be given if patients are experiencing 2 or more attacks per month. Modern treatment is effective in about 60% of patients.
- NICE advise either topiramate or propranolol 'according to the person's preference, comorbidities and risk of adverse events'. Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives
- if these measures fail NICE recommend 'a course of up to 10 sessions of acupuncture over 5-8 weeks' or gabapentin
- NICE recommend: 'Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
- for women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- pizotifen is no longer recommend. Adverse effects such as weight gain & drowsiness are common

\*caution should be exercised with young patients as acute dystonic reactions may develop

Question 5 of 195

A 73-year-old man complained of a one day history of blurred vision in the right eye. He has a past history of poorly controlled hypertension and polycythaemia but otherwise enjoys good health. Visual acuity is 6/6 in the left eye and 6/18 in the right eye. Fundoscopy of the right eye is as follows:



What is the most likely diagnosis?

[Ischaemic optic neuropathy20%](#)[Central retinal artery occlusion15%](#)[Papilloedema11%](#)[Central retinal vein occlusion41%](#)[Macular degeneration12%](#)

Central retinal vein occlusion - sudden painless loss of vision, severe retinal haemorrhages on fundoscopy

This slide shows a non-ischaemic central retinal vein occlusion. There are dilated retinal veins and widespread multiple blot haemorrhages.

### **Sudden painless loss of vision**

The most common causes of a sudden painless loss of vision are as follows:

- ischaemic optic neuropathy (e.g. temporal arteritis or atherosclerosis)
- occlusion of central retinal vein
- occlusion of central retinal artery
- vitreous haemorrhage
- retinal detachment

#### Ischaemic optic neuropathy

- may be due to arteritis (e.g. temporal arteritis) or atherosclerosis (e.g. hypertensive, diabetic older patient)
- due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve
- altitudinal field defects are seen

#### Central retinal vein occlusion

- incidence increases with age, more common than arterial occlusion
- causes: glaucoma, polycythaemia, hypertension
- severe retinal haemorrhages are usually seen on fundoscopy

#### Central retinal artery occlusion

- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina

#### Vitreous haemorrhage

- causes: diabetes, bleeding disorders
- features may include sudden visual loss, dark spots

#### Retinal detachment

- features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

#### **Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage**

<b>Posterior vitreous detachment</b>	<b>Retinal detachment</b>	<b>Vitreous haemorrhage</b>
Flashes of light (photopsia) -	Dense shadow that starts	Large bleeds cause sudden



<b>Posterior vitreous detachment</b>	<b>Retinal detachment</b>	<b>Vitreous haemorrhage</b>
in the peripheral field of vision Floaters, often on the temporal side of the central vision	peripherally progresses towards the central vision A veil or curtain over the field of vision Straight lines appear curved Central visual loss	visual loss Moderate bleeds may be described as numerous dark spots Small bleeds may cause floaters

#### Question 1 of 190

An 82-year-old female is brought into your falls clinic by her daughter after her third fall this year. No fractures were sustained and she appears to have no significant head injuries. The fall appears mechanical in nature. She currently lives with her daughter, who reports the patient's mobility to be progressively deteriorating, from full independence and no exercise limitations 1 year ago to restrictions at 50-70 yards now, limited by knee pain secondary to osteoarthritis. Her other past medical history includes hypertension, type 2 diabetes mellitus, chronic kidney disease and previous gallstones.

You note she is withdrawn and makes little eye contact. Her voice is quiet. When you ask her whether she is low in mood, she does not respond. She reports no suicidal ideations but has little hope for the future. She asks you to 'not worry about it', as she 'has been the same way for several months now'. However, the patient does seem amenable to some kind of treatment.

On the Beck depression scale, she scores 11/63 (0-13 = no or minimal depression), on the geriatric depression scale, she scores 11/15 (greater than 10 = indicative of depression) and mini-mental state examination, she scores 19/30 (20-26 = mild cognitive impairment, 10-19 = moderate cognitive impairment). Routine investigations including B12, folate, thyroid function, liver function tests and bone profile are unremarkable.

What is the most appropriate treatment pathway?

[Citalopram39%](#) [Amitriptyline6%](#) [Mirtazapine24%](#) [Donepezil22%](#) [No treatment required9%](#)

Depression in elderly can depress cognitive function, hence cognition may be inaccurately depressed on measurement scales. Donepezil is thus not indicated on this measure alone. In elderly patients, GDS is more appropriate than Beck's depression scale, as the latter focuses heavily on somatic symptoms that frequently under-score depression in elderly patients. This patient is describing depression without suicidal ideations. Tricyclic antidepressants and SSRIs are similarly efficacious in elderly patients but the first line of treatment for depression in the elderly is a SSRI such as citalopram, mainly due to the lack of interactions with primarily P450 enzymes<sup>1</sup>. TCAs produce significantly greater anticholinergic side effects. Mirtazapine and sertraline failed to demonstrate a significant benefit compared to placebo in Alzheimer's patients

with depression.

1. Rodda J, Walker Z, Carter J. Depression in older adults. BMJ 2011; 34:d5219

## **Depression in older people**

Older patients are less likely to complain of depressed mood

### Features

- physical complaints (e.g. hypochondriasis)
- agitation
- insomnia

### Management

- SSRIs are first line (adverse side-effect profile of TCAs more of an issue in the elderly)

### Question 2 of 190

A 55-year-old man is reviewed in psychiatric clinic. He has been referred by his GP who has been unable to manage his depression. He has a past medical history of hypertension, previous acute coronary syndrome one year ago, high cholesterol and depression. He mentions that his mood has worsened and that he is having persistent thoughts about taking his own life to the point where he is scared that he might 'do something'. There are no effects on his cognition, concentration or any sleep disturbance. What advice should he be given in regards to driving?

[No restrictions on driving27%](#)[No restrictions on driving but must inform the DVLA14%](#)[Can drive a car but not lorry or bus9%](#)[Can drive a car but not lorry or bus and must inform the DVLA13%](#)[Must not drive and must inform the DVLA37%](#)

The correct answer is that he must not drive and must inform the DVLA. He is a patient with depression and active suicidal thoughts and therefore should not drive.

## **DVLA: psychiatric disorders**

The below rules apply to group 1 vehicles (car and motorcycle), the group 2 (bus and lorry) rules are stricter.

### **Specific rules**

- Severe anxiety or depression with any of the following: significant memory problems, significant concentration problems, agitation, behavioural disturbance or suicidal thoughts: must not drive and must notify the DVLA
- Acute psychotic disorder: must not drive during acute illness and must notify the DVLA
- Hypomania or mania: must not drive during acute illness and must notify the DVLA
- Schizophrenia: must not drive during acute illness and must notify the DVLA
- Pervasive developmental disorders and ADHD: may be able to drive but must inform the DVLA
- Mild cognitive impairment: may drive and need not inform the DVLA
- Dementia: may be able to drive but must inform the DVLA
- Mild learning disability: may be able to drive but must inform the DVLA
- Severe disability: must not drive and must notify the DVLA
- Personality disorders: may be able to drive but must inform the DVLA

Source:

'Assessing Fitness to Drive a Guide for Medical Professionals.' Driver and Vehicle Licensing Agency (2016): n. pag. Web. data/file/526635/assessing-fitness-to-drive-a-guide-for-medical-professionals.pdf>

### **Question 3 of 190**

A 23-year-old female has presented 2 days after discharge from the neurology team with a constant diffuse headache, worse on standing than lying down, without neck stiffness or photophobia, but associated with nausea and vomiting. 48 hours ago, she was an inpatient being investigated for intermittent headaches over the past 8 months, typically over the left side of her frontal and temporal regions, of sudden onset during any time of day, associated with double vision, lasting for 'hours' at a time. She was experiencing up to 5 episodes a week, with one episode witnessed during her admission, when the senior house officer noted bilateral restriction in vertical eye movements, adduction and unreactive pupils, spontaneously resolving after 3 hours. Her blood tests were unremarkable.

The patient underwent a CT head, demonstrating no intracranial lesions; and a lumbar puncture:

Opening pressure 12.3 cmH<sub>2</sub>O  
WCC 2 /mm<sup>3</sup>  
RBC 50 /mm<sup>3</sup>  
Protein 0.45 g/l  
Glucose 4.5 mmol/l (serum 6.7 mmol/l)  
Oligoclonal bands None present

The patient subsequently self-discharged, reporting no immediate headaches, back pain or lower limb paraesthesia after the lumbar puncture.

During this second admission, she undergoes an MRI head scan, demonstrating significant diffuse meningeal enhancement and bilateral shallow subdural haemorrhages. What is the appropriate treatment?

[Oral fluids, caffeine and blood patch49% Repeat lumbar puncture6% Intravenous aciclovir15% Intravenous ceftriaxone6% Neurosurgical input23%](#)

There are two headaches here: the initial presentation appears to be an unusual migrainous phenomenon, possibly ophthalmoplegic migraine, while the second is clearly a low-pressure headache. The neurologists would have been correct in initially ruling out any other possible causes of ocular paresis with a lumbar puncture but the CSF constituents are fairly unremarkable.

Do not be alarmed by the report of the MRI head: meningeal enhancement, thickening and shallow subdural haematoma are features of low-pressure headaches and do not represent meningitis or subdural haematomas regarding neurosurgical drainage. A repeat lumbar puncture would make exacerbate the problem and hence inappropriate. In view of the low-pressure headache occurring soon after a lumbar puncture, encouraging oral fluids, caffeine and a blood patch by the anaesthetists would be most appropriate.

### **Post-lumbar puncture headache**

Headache following lumbar puncture (LP) occurs in approximately one-third of patients. The pathophysiology of is unclear but may relate to a 'leak' of CSF following dural puncture. Post-LP headaches are more common in young females with a low body mass index

Typical features

- usually develops within 24-48 hours following LP but may occur up to one week later
- may last several days
- worsens with upright position

- improves with recumbent position

#### **Factors which may contribute to headache      Factors which do not contribute to headache**

Increased needle size  
Direction of bevel  
Not replacing the stylet  
Increased number of LP attempts

Increased volume of CSF removed  
Bed rest following procedure  
Increased fluid intake post procedure  
Opening pressure of CSF  
Position of patient

#### **Management**

- supportive initially (analgesia, rest)
- if pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma
- treatment options include: blood patch, epidural saline and intravenous caffeine

#### **Question 4 of 190**

A 59-year-old woman is referred by her GP to neurology clinic for assessment. The patient describes intermittent episodes of pain affecting the left side of her face. She recalls the first attack vividly as a sudden onset of severe 'electric-shock' pain coming on suddenly around one year previously as she had cleaned her teeth with her electric toothbrush. The pain was felt around the cheek extending down to the jaw-line. The first attack had lasted several hours and she had ultimately attended her dentist and received a filling to a left molar tooth. While symptoms from that episode had resolved, she had then suffered from similar episodes at increasing frequency, approximately every fortnight over the last couple of months. These attacks had on occasion been unprovoked but were sometimes induced by stimulation of the affected area or cold winds. The patient was tearful as she recounted the negative impact her symptoms had had on her lifestyle. There was no history of headaches, sinus symptoms or seizures.

The patient had a fairly unremarkable past-medical history, notable only for hypothyroidism and long-standing struggles to avoid overweight. Her only regular medication was thyroxine 125 micrograms daily and the patient reported no allergies. There was no family history of neurological disease. The patient worked as a law clerk and did not smoke or drink significant alcohol.

Examination demonstrated an unremarkable cranial nerve and peripheral nerve examinations. In particular, colour vision, visual acuity and hearing were normal.

What is the correct first line management of the patient's symptoms?

[Gabapentin10% Carbamazepine72% Pregabalin8% Baclofen4% Lamotrigine5%](#)

The patient reports a classical history of trigeminal neuralgia. Notable features are the memorable first occurrence, attacks precipitated by touch or vibration and the history of inappropriate dental treatment. Time between attacks often gradually reduces leaving patients quality of life significantly impaired.

The patient has no other symptoms or neurological signs that might suggest an alternative diagnosis such as multiple sclerosis, sinusitis or a space-occupying lesion. In the presence of such features, an MRI brain is the most appropriate investigation.

Carbamazepine is the only drug licensed specifically for trigeminal neuralgia in the UK. In 70 % of patients it provides initial 100 % pain relief. However, caution must be used due to side-effects and drug interactions. Oxcarbazepine is a derivative of carbamazepine with similar efficacy but improved tolerability and side-effect profile.

In the evidence of allergy or intolerance to the above drugs then use of baclofen or lamotrigine should be considered, however the evidence base for both is thin. Gabapentin in combination with ropivacaine injections did show benefit in one randomised controlled trial but this result has not been replicated in subsequent investigations. Pregabalin had reported effectiveness in one prospective study of 53 patients.

Zakrzewska J, Linskey M. Trigeminal neuralgia. BMJ 2014;348:g474.

## **Trigeminal neuralgia**

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur

The International Headache Society defines trigeminal neuralgia as:

- a unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
- the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- the pains usually remit for variable periods

## **Management**

- carbamazepine is first-line
- failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

#### Question 5 of 190

A 54-year-old female attends her GP with sudden onset reduced vision. This is particular to the left eye. The patient has a background of type 2 diabetes mellitus and hypertension. The GP is unable to adequately see the optic fundi on fundoscopy but thinks the left side appears pale.

What is the most likely diagnosis?

[Retinal vein occlusion18%](#)[Hypertensive retinopathy6%](#)[Giant cell arteritis7%](#)[Stroke4%](#)[Retinal artery occlusion65%](#)

Retinal artery occlusion is associated with cardiovascular risk factors as in this case. It causes sudden onset painless visual loss. Fundoscopy may reveal a pale retina and the macula can appear as a 'cherry red spot'.

Retinal vein occlusion may present with distorted and blurred vision rather than visual loss. Additionally, fundoscopy may reveal vascular dilatation with associated haemorrhages.

Hypertensive retinopathy tends to be asymptomatic and is instead generally an indicator of end-organ damage due to long-term effects of hypertension.

Giant cell arteritis may be expected to have preceding symptoms of headache, jaw pain and scalp tenderness before abrupt visual loss.

#### Question 6 of 190

A 44 year-old man presents to the neurology clinic. He complains of weakness in the right hand, which causes difficulty with tasks such as writing and dressing, and has also noted 'twitching' in his right forearm and hand. He cannot recall exactly when the symptoms first began but feels that they have certainly been present for at least six months, and that they have got worse.

He is otherwise fit and well. His only past medical history is well-controlled asthma. There is no family history of neurological disease.

Cranial nerve examination is normal. On examination of the right hand, there is weakness of

extension of the the middle and ring fingers (2/5 on the MRC scale), but no discernible muscle wasting. Fasciculations are visible in the dorsal aspect of the forearm. On examination of the left hand, there is also some subtle weakness of extension of the ring finger (4/5 on the MRC scale). There is no weakness of wrist extension on either side and power in all other muscle groups is normal. For both hands, all the fingers extend when the wrist is passively moved into palmar flexion. All reflexes are normal and there are no sensory signs.

What is the most likely diagnosis?

[Multifocal motor neuropathy39%](#)[Chronic inflammatory demyelinating polyneuropathy10%](#)[Motor neuron disease \(amyotrophic lateral sclerosis\)32%](#)[Inclusion body myositis13%](#)[Ruptured tendon of extensor digitorum6%](#)

The history is typical for multifocal motor neuropathy (MMN). The condition presents with asymmetric muscle weakness, which is slowly progressive, and without sensory signs. Differential weakness of finger extension is a typical presentation, and reflects a pathological process which selectively affects particular motor fibres within a peripheral nerve (in this case the posterior interosseous branch of the radial nerve). Weakness without wasting is another typical feature. Nerve conduction studies show areas of conduction block outside usual areas for compression. Intravenous immunoglobulin can produce a rapid improvement in weakness.

MMN may sometimes mimic motor neuron disease (MND). Both feature weakness, wasting, and fasciculation, with relatively preserved reflexes, and normal sensation. However, certain features suggest one diagnosis over the other. For example, bulbar weakness is common in MND but rare in MMN. Depending on the form of MND, variable upper motor neuron signs may occur, contrary to MMN which is a purely lower motor neuron condition occurring in a distribution correlating with named peripheral nerves. Finally, whereas MND is usually fatal within 5 years, MMN is slowly progressive over decades and does not typically cause respiratory failure.

Chronic inflammatory demyelinating polyneuropathy(CIDP) typically causes a progressive sensory and motor neuropathy with loss of reflexes. CSF protein is elevation and nerve conduction studies show evidence of demyelination.

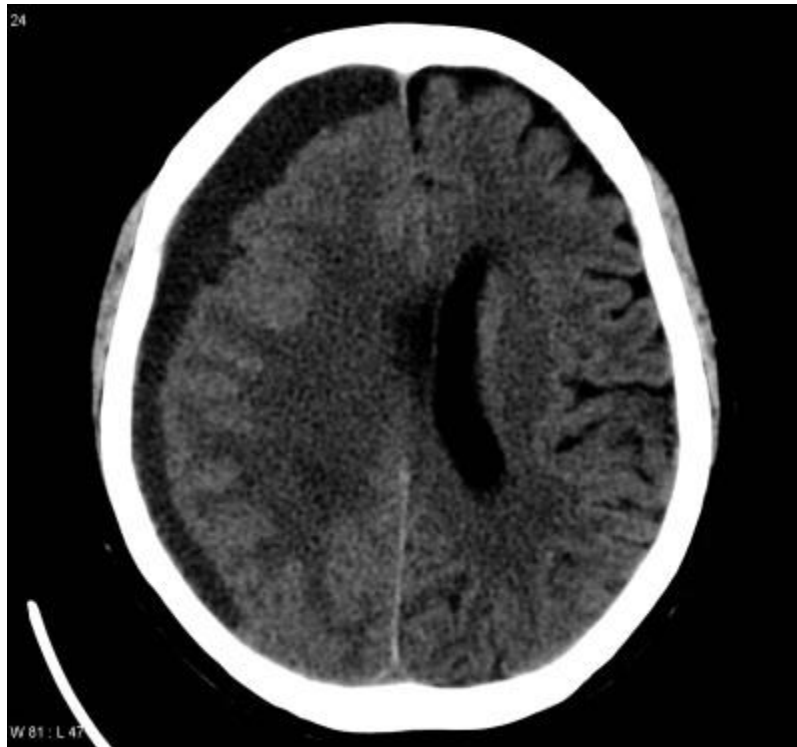
Inclusion body myositis characteristically causes weakness of finger flexion, as well as knee extension and ankle dorsiflexion. Affected muscles are wasted, and fasciculations do not occur as there is no denervation.

Rupture of extensor tendons often occurs in rheumatoid arthritis. The affected finger cannot be actively extended, and does not passively extend when the wrist is passively moved into palmar flexion.



A 73-year-old man who is a chronic alcoholic is brought to the Emergency Department by an ambulance. He was found collapsed in the street. On admission his airway, breathing and circulation are satisfactory. His GCS is 13/15 (eyes = 3, verbal = 4, movement = 6) although his level of consciousness appears to be fluctuating. There are no obvious signs of external head injury.

A CT head (without contrast) is performed:



© Image used on license from [Radiopaedia](#)

What is the most likely diagnosis?

[Subarachnoid haemorrhage](#)6%[Wernicke's encephalopathy](#)5%[Subdural haematoma](#)76%[Meningioma](#)4%[Extradural haematoma](#)9%

CT scan demonstrates a right sided chronic subdural haemorrhage resulting in midline shift.

**Head injury: types of traumatic brain injury**

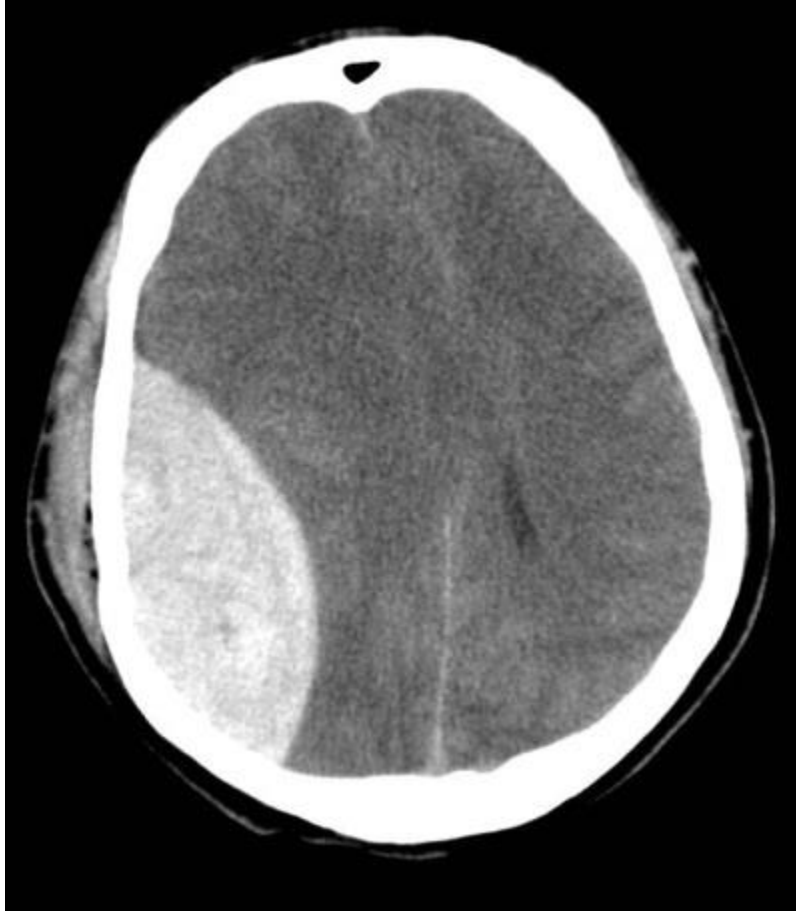
## Basics

- primary brain injury may be focal (contusion/haematoma) or diffuse (diffuse axonal injury)
- diffuse axonal injury occurs as a result of mechanical shearing following deceleration, causing disruption and tearing of axons
- intra-cranial haematomas can be extradural, subdural or intracerebral, while contusions may occur adjacent to (coup) or contralateral (contre-coup) to the side of impact
- secondary brain injury occurs when cerebral oedema, ischaemia, infection, tonsillar or tentorial herniation exacerbates the original injury. The normal cerebral auto regulatory processes are disrupted following trauma rendering the brain more susceptible to blood flow changes and hypoxia
- the Cushing's reflex (hypertension and bradycardia) often occurs late and is usually a pre terminal event

Type of injury	Notes
<b>Extradural (epidural) haematoma</b>	<p>Bleeding into the space between the dura mater and the skull. Often results from acceleration-deceleration trauma or a blow to the side of the head. The majority of extradural haematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery.</p> <p>Features</p> <ul style="list-style-type: none"><li>• features of raised intracranial pressure</li><li>• some patients may exhibit a lucid interval</li></ul>
<b>Subdural haematoma</b>	<p>Bleeding into the outermost meningeal layer. Most commonly occur around the frontal and parietal lobes.</p> <p>Risk factors include old age, alcoholism and anticoagulation.</p> <p>Slower onset of symptoms than a extradural haematoma.</p>
<b>Subarachnoid haemorrhage</b>	<p>Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury</p>

## Image gallery

Extradural (epidural) haematoma:



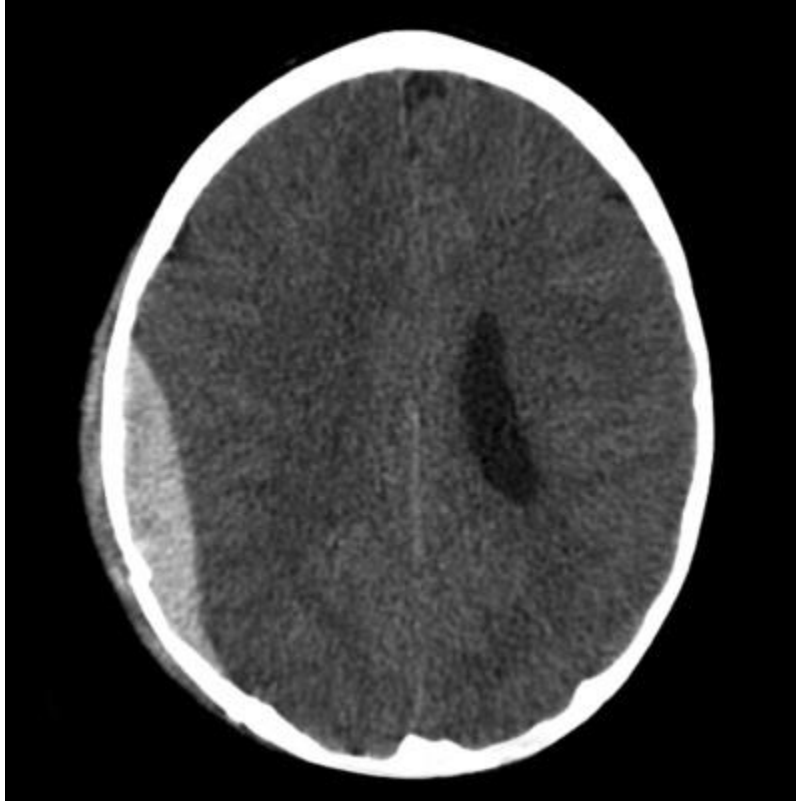
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Subdural haematoma:



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Subarachnoid haemorrhage:



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### Question 1 of 183

A 45 year old man develops weakness of the extensors in the wrist and digits of his left upper limb over a week. Over the next 2 months he also notices weakness of the small muscles of hands on the right side, and that he is progressively unable to dorsiflex his right foot. On examination, he has wasting and 2/5 power in the left wrist and digit extensors. On the right he has clawing of the right ring and little fingers along with wasting of the small muscles of the hand on that side (except the thenar eminence and the first two lumbricals, which are spared). He has a right foot drop along with wasting of the anterior tibial and perineal muscles on that side. Fasciculations are seen in all of the areas of weakness. Sensory examination and reflexes are normal, along with no clonus. Plantars are down-going. The remainder of the examination are normal. Nerve conduction studies show conduction block. What is first-line maintenance treatment for this condition?

[Riluzole 45% Intravenous immunoglobulin 25% Pyridostigmine 7% Steroids 16% Beta-interferon 8%](#)

The answer here is the condition called multifocal motor neuropathy with conduction block (MMNCB). These patients are usually younger to middle-aged men who develop focal arm weakness in the distribution of a named nerve. It usually happens quite suddenly (e.g. over a week) and they are often mistaken as a stroke at first presentation. However, over several months additional named motor nerves become involved asymmetrically such that MMNCB may eventually look like motor neurone disease (MND) - the principle differential here (specifically the lower motor neurone progressive muscular atrophy form rather than the mixed upper/lower motor neurone ALS form). For exam purposes, the key difference between these two conditions is the nerve conduction studies. MMNCB shows conduction block. MND does not. MMNCB is a demyelinating condition, much in the same way Guillain Barré or chronic inflammatory demyelinating polyneuropathy (CIDP) are. However, in MMNCB this demyelination is in segments of a nerve rather than affecting the whole nerve. Therefore, the action potentials (as well as being slowed because of demyelination) actually don't get past the areas of conduction block. The importance of doing nerve conduction studies is to decide whether a motor neuropathy is axonal (i.e. the axon itself getting damaged) or demyelinating. The demyelinating ones tend to be more easily and similarly treatable. MMNCB, Guillain Barré, and CIDP are all good examples of demyelinating neuropathies, all of which therefore respond to intravenous immunoglobulin (IVIG).

Note that the nerves involved in this particular case are the left radial nerve, right ulnar nerve, and right common peroneal nerve.

Reference: Andrew Tarulli. Neurology: A Clinician's Approach. Cambridge University Press; 1 edition (18 Nov. 2010)

## **Multifocal motor neuropathy**

Acquired autoimmune demyelinating motor neuropathy

Associated with motor conduction block

Slowly progressive, distal motor neuropathy which progresses over many years

Anti-GM1 antibodies frequently raised

Question 2 of 183

A 70-year-old man with a history of hypertension and benign prostatic hypertrophy is brought in by ambulance after a fall. He reports he felt dizzy after standing up from his arm chair, stumbled

and tripped over his cat. His wife, who witnessed the fall, reports that he then hit his head on the coffee table and lost consciousness for around 1 minute.

She describes no abnormal movements or incontinence. On regaining consciousness he was oriented immediately. He remembers regaining consciousness. He has no headache, dizziness, nausea or vomiting.

On examination, he has a small laceration on his forehead. His pupils were equal and reactive to light. He had no focal neurological deficits. He was a 15 on the Glasgow Coma Scale. His abbreviated mental test score was 10/10.

ECG: Sinus rhythm. 70 beats per minute. No T wave or ST segment changes.

Blood pressure (lying): 135/75 mmHg

Blood pressure (standing): 110/60 mmHg

Haemoglobin 135 g/dl

Troponin T 1 ng/L

Urine dip: trace of protein

What is the most appropriate course of action?

[Admit for CT head within 1 hour14%](#)[Admit for CT head within 8 hours44%](#)[Admit for CT head within 24 hours16%](#)[Discharge to return for CT head next day6%](#)[Discharge with outpatient follow-up, no imaging required21%](#)

Nice Guidelines on head injury state that:

'For adults who have sustained a head injury and have any of the following risk factors, perform a CT head scan within 1 hour of the risk factor being identified:

- GCS less than 13 on initial assessment in the emergency department.
- GCS less than 15 at 2 hours after the injury on assessment in the Emergency Department.
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- Post-traumatic seizure.
- Focal neurological deficit.
- More than 1 episode of vomiting.'

The patient does not meet any of these criteria, so CT head within 1 hour is not mandatory.

The guideline then also states:

'For adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury, perform a CT head scan within 8 hours of the head injury:

- Age 65 years or older.
- Any history of bleeding or clotting disorders.
- Dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs).
- More than 30 minutes' retrograde amnesia of events immediately before the head injury.'

As this gentleman had a period of unconsciousness and is over 65, he should have a CT head within 8 hours.

### **Head injury: NICE guidance on investigation**

NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging. The latter group are also divided into two further cohorts, those who require an immediate CT head and those requiring CT head within 8 hours of injury:

#### **CT head immediately**

- GCS < 13 on initial assessment
- GCS < 15 at 2 hours post-injury
- suspected open or depressed skull fracture.
- any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- post-traumatic seizure.
- focal neurological deficit.
- more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- age 65 years or older
- any history of bleeding or clotting disorders
- dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs)

- more than 30 minutes' retrograde amnesia of events immediately before the head injury

If a patient is on warfarin who have sustained a head injury with no other indications for a CT head scan, perform a CT head scan within 8 hours of the injury.

#### Question 1 of 181

A 37-year-old Japanese female presents with her second episode of loss of colour vision and significant visual acuity impairment in both eyes. Three days later, she complains of vomiting, acute urinary retention, requiring urinary catheter insertion, and inability to move either leg. On examination, she was unable to correctly name any Ishihara plates. An MRI of her brain and spine demonstrates multiple hyperintense T2 white matter lesions in her spine suggestive of demyelination, one of which extends from C5 to T1. Which investigation confirms the diagnosis?

[Lumbar puncture for oligoclonal bands18%](#) [Repeat MRI spine with diffusion weighting7%](#) [Serum aquaporin 4 antibody56%](#) [Serum anti-NMDA antibody9%](#) [Repeat MRI spine with gadolinium contrast10%](#)

The patient has presented with optic neuritis, myelitis and vomiting, strongly suggestive of a diagnosis of neuromyelitis optica (NMO), also known as Devic's disease.

In this case, CSF oligoclonal bands neither confirms nor excludes a diagnosis MRI spine with DWI would demonstrate acute ischaemic infarcts if a spinal stroke was suspected. Gadolinium enhanced imaging does not add to the diagnostic criteria for NMO. Anti-NMDA antibody is a serum autoantibody for a subtype of autoimmune encephalitis.

### Neuromyelitis optica

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder. Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations<sup>1</sup>. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria<sup>2</sup>:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

Question 2 of 181

The patient below is being treated for epilepsy:



© Image used on license from [DermNet NZ](#) and with the kind permission of Prof Raimo Suhonen

What is the most likely underlying diagnosis?

[HIV](#)6% [Neurofibromatosis](#)9% [Arteriovenous malformation](#)7% [Tuberous sclerosis](#)61% [Lennox-Gastaut syndrome](#)16%

These skin lesions represent adenoma sebaceum.

## Tuberous sclerosis

Tuberous sclerosis (TS) is a genetic condition of autosomal dominant inheritance. Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

### Cutaneous features

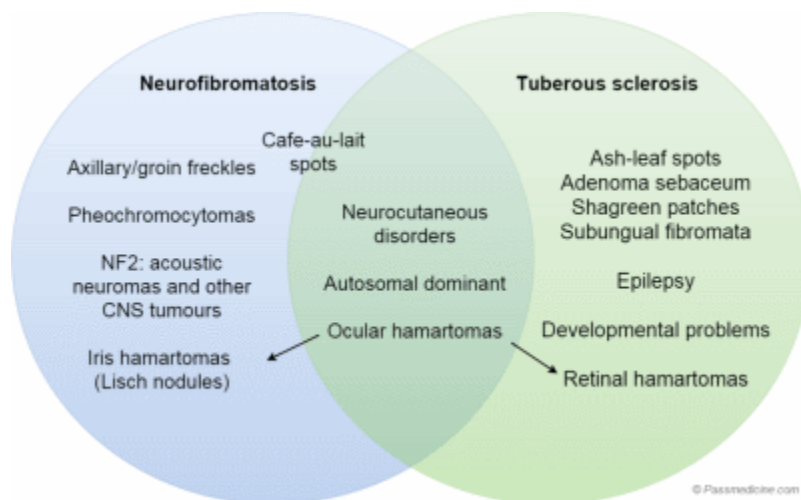
- depigmented 'ash-leaf' spots which fluoresce under UV light
- roughened patches of skin over lumbar spine (Shagreen patches)
- adenoma sebaceum (angiofibromas): butterfly distribution over nose
- fibromata beneath nails (subungual fibromata)
- café-au-lait spots\* may be seen

### Neurological features

- developmental delay
- epilepsy (infantile spasms or partial)
- intellectual impairment

### Also

- retinal hamartomas: dense white areas on retina (phakomata)
- rhabdomyomas of the heart
- gliomatous changes can occur in the brain lesions
- polycystic kidneys, renal angiomyolipomata
- lymphangiomyomatosis: multiple lung cysts



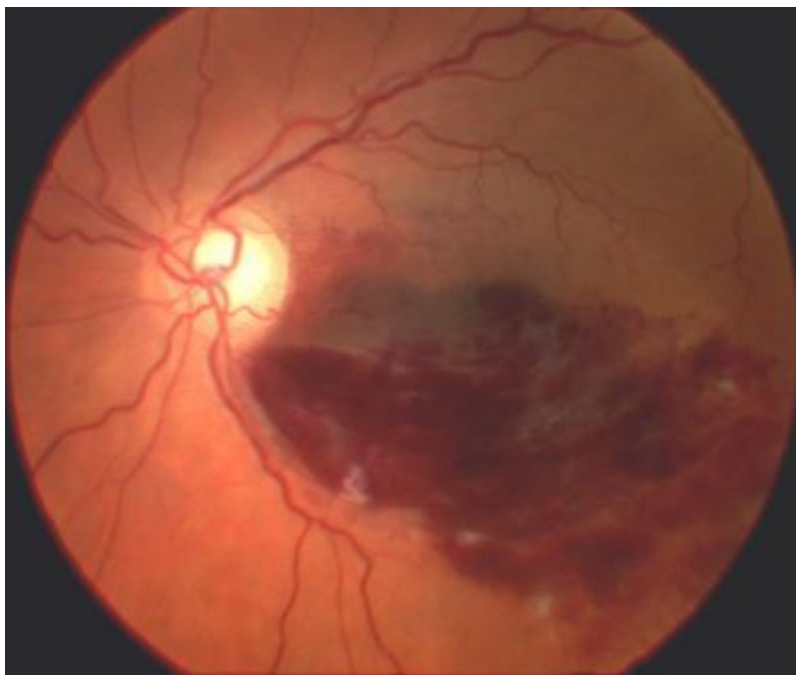


Comparison of neurofibromatosis and tuberous sclerosis. Note that whilst they are both autosomal dominant neurocutaneous disorders there is little overlap otherwise

\*these of course are more commonly associated with neurofibromatosis. However a 1998 study of 106 children with TS found café-au-lait spots in 28% of patients

Question 3 of 181

A man presents with a sudden worsening of his vision in the right eye.



What does fundoscopy show?

[Vitreous haemorrhage45%](#)[Branch retinal vein occlusion38%](#)[Choroidal naevus7%](#)[Retinoschisis5%](#)[Retinal detachment6%](#)

Fundoscopy shows flame-shaped haemorrhages on the temporal aspect of the fundus and subretinal haemorrhages.



## **Sudden painless loss of vision**

The most common causes of a sudden painless loss of vision are as follows:

- ischaemic optic neuropathy (e.g. temporal arteritis or atherosclerosis)
- occlusion of central retinal vein
- occlusion of central retinal artery
- vitreous haemorrhage
- retinal detachment

### Ischaemic optic neuropathy

- may be due to arteritis (e.g. temporal arteritis) or atherosclerosis (e.g. hypertensive, diabetic older patient)
- due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve
- altitudinal field defects are seen

### Central retinal vein occlusion

- incidence increases with age, more common than arterial occlusion
- causes: glaucoma, polycythaemia, hypertension
- severe retinal haemorrhages are usually seen on fundoscopy

### Central retinal artery occlusion

- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina

### Vitreous haemorrhage

- causes: diabetes, bleeding disorders
- features may include sudden visual loss, dark spots

### Retinal detachment

- features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

## Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage

Posterior vitreous detachment	Retinal detachment	Vitreous haemorrhage
Flashes of light (photopsia) - in the peripheral field of vision Floaters, often on the temporal side of the central vision	Dense shadow that starts peripherally progresses towards the central vision A veil or curtain over the field of vision Straight lines appear curved Central visual loss	Large bleeds cause sudden visual loss Moderate bleeds may be described as numerous dark spots Small bleeds may cause floaters

### Question 5 of 181

A 41 year old lady with a background of vitiligo and pernicious anaemia presents with weakness largely affecting her shoulders and hip muscles. The problem is variable throughout the day dependent on how much activity she has done. She does feel that symptoms are at their worst at the end of the day, when indeed her family also say her voice becomes quieter. Clinical examination demonstrates proximal muscle weakness after repeated testing. Electromyography demonstrates a decline in the amplitude of successive potentials (decremental response). Antibodies to the acetylcholine receptor (AChR) are negative on serum testing. Her CT thorax is normal. Which of the following is likely to be most helpful in establishing a diagnosis?

[Anti-smooth muscle antibodies4%](#) [Anti-muscle specific kinase \(MuSK\) antibodies79%](#) [Anti-striated muscle antibody6%](#) [Anticardiolipin antibodies5%](#) [Anti-transglutaminase antibodies6%](#)

The diagnosis here is Myasthenia Gravis (MG). Most (but not all) patients with MG are seropositive for the acetylcholine receptor (AChR) antibody. Antibodies to muscle-specific receptor tyrosine kinase (MuSK), a surface membrane component essential in the development of the neuromuscular junction, have recently been identified and are found in up to 50% of MG patients who are seronegative for AChR antibodies. Emerging data suggests that the patterns of weakness and response to certain treatments may be different from those with AChR positive MG. Anti-striated muscle antibody usually positive in MG patients that have a thymoma.

Don't forget to recognise the autoimmune past medical history in this patient. It often gives useful diagnostic clues that the underlying condition is also an autoimmune one.

Ref: [www.myasthenia.org/healthprofessionals/clinicaloverviewofmg.aspx#sthash.dCo1qtr5.dpuf](http://www.myasthenia.org/healthprofessionals/clinicaloverviewofmg.aspx#sthash.dCo1qtr5.dpuf)

## Myasthenia gravis

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases\*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

### Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

### Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

### Management

- long-acting anticholinesterase e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

## Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

\*antibodies are less commonly seen in disease limited to the ocular muscles

## Question 6 of 181

A 32-year-old female presents with four episodes of loss of consciousness within the past 4 weeks. She denies palpitations or chest pain but reports sudden onset binocular black dots in visual fields, occasional flashing lights, dysarthria and hearing loss, all of which resolves after about 60 minutes. She is unsure about the relevance of an occipital headache, onset with frequency of about three times per week for the past year. She denies any limb weakness, altered sensation or facial droop. She has no past medical history or family history of epilepsy. Your neurological examination, including fundoscopy is unremarkable. An EEG is unremarkable. What is the likely diagnosis?

[Cluster headache6%](#) [Transient ischaemic attacks9%](#) [Basilar migraine76%](#) [Bilateral retinal detachment5%](#) [Guillain-Barre syndrome5%](#)

The symptoms are most likely to represent a rare migraine subtype with aura known as basilar migraine. A large Danish study identified up to 10% of all non-hemiplegic migraineurs as basilar migraines, most of whom report a brainstem-associated range of symptoms lasting for around one hour<sup>1</sup>. 61% of patients report vertigo and over half dysarthria. One in four report episodes of loss of consciousness. Investigations include 24 hour tape and echocardiogram to exclude cardiac syncope and MRI to exclude posterior fossa space occupying lesion. An EEG may not exclude posterior epileptiform activity. Prevention can be offered with verapamil or topiramate.

1. Kirchmann M, Thomsen LL, Olesen J. Basilar-type migraine: clinical, epidemiologic, and genetic features. *Neurology*. 2006;66(6):880

## Migraine: diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for migraine without aura:

Point	Criteria
<b>A</b>	At least 5 attacks fulfilling criteria B-D
<b>B</b>	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated) Headache has at least two of the following characteristics:
<b>C</b>	<ul style="list-style-type: none"> <li>1. unilateral location*</li> <li>2. pulsating quality (i.e., varying with the heartbeat)</li> <li>3. moderate or severe pain intensity</li> <li>4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)</li> </ul> <p>During headache at least one of the following:</p>
<b>D</b>	<ul style="list-style-type: none"> <li>1. nausea and/or vomiting*</li> <li>2. photophobia and phonophobia</li> </ul>
<b>E</b>	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

\*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (seen in around 25% of migraine patients) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

If we compare these guidelines to the **NICE criteria** the following points are noted:

- NICE suggests migraines may be unilateral or bilateral
- NICE also give more detail about typical auras:

Auras may occur with or without headache and:

- are fully reversible
- develop over at least 5 minutes
- last 5-60 minutes

The following aura symptoms are atypical and may prompt further investigation/referral;

- motor weakness
- double vision

- visual symptoms affecting only one eye
- poor balance
- decreased level of consciousness.

#### Question 1 of 175

A 32-year-old male presents with a sudden onset left sided weakness with new onset expressive dysphasia and dress apraxia. He has a seven year history of progressive cognitive impairment and seizures, lives in sheltered accommodation and was brought in after his relatives, who visit him on a weekly basis, noted a change from his baseline. The patient is a poor historian and could not remember the duration of symptoms. He reports a recent history of burning sensation when passing urine associated with increased frequency and reduced oral intake for the past four days. An MRI head demonstrates multiple areas of ischaemia within left and right cortex inconsistent with one single vascular territory. A urine dip is positive for leucocytes and nitrites, negative for ketones. A venous blood gas is taken:

pH                7.15  
PaCO<sub>2</sub>        2.4 kPa  
Bicarbonate 6 mmol/l  
Lactate        18 mmol/l  
Anion gap    16 mmol/l

What is the unifying diagnosis?

[MELAS66%Diabetic ketoacidosis6%Ingestion of antifreeze11%Severe dehydration secondary to urosepsis10%Metformin induced lactic acidosis7%](#)

Young patients with significant cognitive impairment should raise suspicion. This patient presents with a significant lactic acidosis, with low bicarbonate likely secondary to chronic neutralisation in the presence of systemic acidosis. Multiple ischaemic infarcts inconsistent with vascular territories are suspicious of a metabolic disorder within the brain parenchyma. In this case, a mitochondrial genetic condition, mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS), is most likely. Focal and generalised seizures are common for MELAS patients, as is early onset dementia, focal weakness and cortical blindness from multiple ischaemic stroke episodes. Symptoms normally present at late childhood and early adulthood, with patients develop normally until then. Diagnosis is made through lactic acidosis, a progressive neurological and dementing clinical course and muscle biopsy for ragged red fibres. The majority of patients have been linked to an underlying mutation in transfer RNA<sup>1</sup>.

In this case, the UTI is a red herring. While the patient may have a UTI, it does not produce a

unifying diagnosis of cerebral and metabolic abnormalities. A normal anion gap rules out ingestion of inorganic acids or DKA. The patient is negative for urinary ketones. There is no suggestion he takes metformin.

1. Montagna P, Gallassi R, Medori R, Govoni E, Zeviani M, Di Mauro S, Lugaesi E, Andermann F. MELAS syndrome: characteristic migrainous and epileptic features and maternal transmission. *Neurology*. 1988;38(5):751

## **Mitochondrial diseases**

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally encode rare neurological diseases
- poor genotype:phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

## **Histology**

- muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples include:

- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

## Question 2 of 174

A 64-year-old man is reviewed in the neurology clinic after being referred with a tremor. The neurologist concludes that his symptoms and clinical findings are intermediate and it is not clear whether they are caused by essential tremor or Parkinson's disease. Which one of the following investigations would help reach a definite diagnosis?

[Structural MRI](#)17%[Acute levodopa challenge](#)17%[<sup>123</sup>I-FP-CIT single photon emission computed tomography \(SPECT\)](#)58%[Magnetic resonance spectroscopy](#)8%[Magnetic resonance volumetry](#)0%

<sup>123</sup>I-FP-CIT SPECT can be used to help differentiate essential tremor from Parkinson's

NICE recommend:

*Consider <sup>123</sup>I-FP-CIT single photon emission computed tomography (SPECT) for people with tremor if essential tremor cannot be clinically differentiated from parkinsonism.*

## Parkinson's disease: features

Parkinson's disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.. This results in a classic triad of features: bradykinesia, tremor and rigidity. The symptoms of Parkinson's disease are characteristically asymmetrical.

### Epidemiology

- around twice as common in men
- mean age of diagnosis is 65 years

### Bradykinesia

- poverty of movement also seen, sometimes referred to as hypokinesia
- short, shuffling steps with reduced arm swinging
- difficulty in initiating movement



## Tremor

- most marked at rest, 3-5 Hz
- worse when stressed or tired
- typically 'pill-rolling', i.e. in the thumb and index finger

## Rigidity

- lead pipe
- cogwheel: due to superimposed tremor

## Other characteristic features

- mask-like facies
- flexed posture
- micrographia
- drooling of saliva
- psychiatric features: depression is the most common feature (affects about 40%); dementia, psychosis and sleep disturbances may also occur
- impaired olfaction
- REM sleep behaviour disorder

**Drug-induced parkinsonism** has slightly different features to Parkinson's disease:

- motor symptoms are generally rapid onset and bilateral
- rigidity and rest tremor are uncommon

Diagnosis is usually clinical. However, if there is difficulty differentiating between essential tremor and Parkinson's disease NICE recommend considering  $^{123}\text{I}$ -FP-CIT single photon emission computed tomography (SPECT).

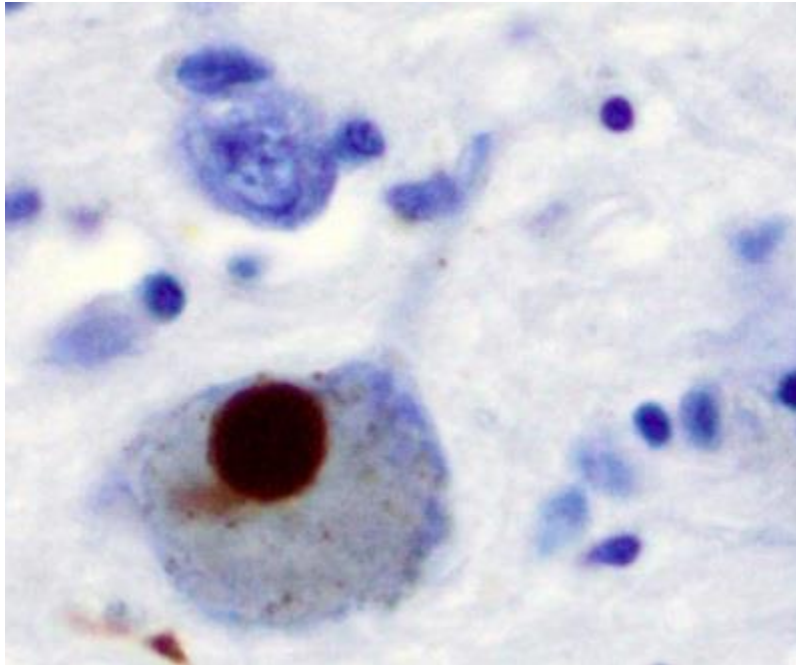


Image sourced from [Wikipedia](#)



A Lewy body (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein.

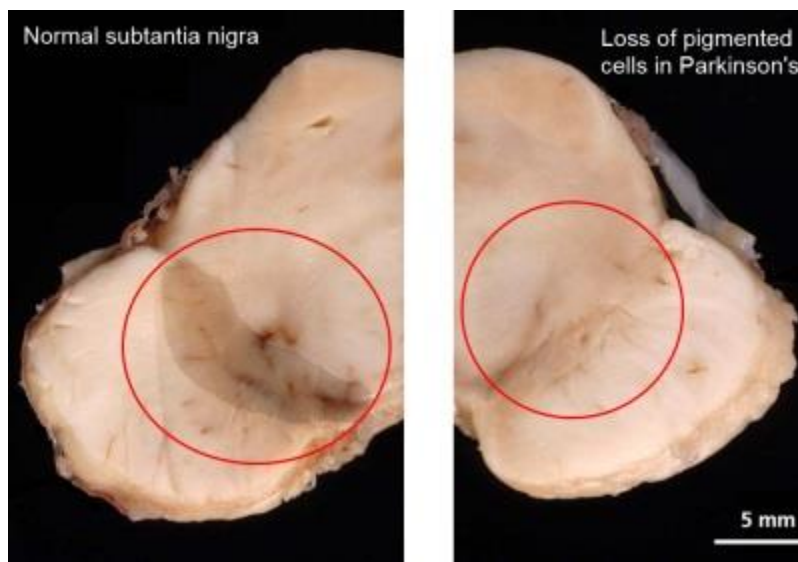


Image sourced from [Wikipedia](#)



Discoloration of the substantia nigra due to loss of pigmented nerve cells.

### Question 1 of 174

A 19-year-old university student is reviewed in the general medical clinic with bilateral ptosis. It has developed gradually over the last few months and has now progressed to the extent that he has to tilt his head upwards during lectures. He denies diurnal variation in his symptoms.

His past medical history is unremarkable and he takes no regular medications. He tells you that his mother had a pacemaker fitted due to frequent 'blackouts'.

On examination, you note the presence of bilateral ptosis. He also has impaired abduction and adduction of both eyes. Direct fundoscopy shows black spicules in the periphery of both eyes. An ECG is taken and shows sinus rhythm with first-degree heart block.

Given the likely diagnosis, which additional symptom is he most likely to describe?

[Night blindness](#)57%[Syncope](#)11%[Tremor](#)10%[Flank pain](#)9%[Diplopia](#)14%

The most likely diagnosis is Kearns-Sayre syndrome, a mitochondrial disorder. Individuals usually present <20 years-of-age with progressive external ophthalmoplegia. Ptosis usually develops first, followed by difficulties with horizontal gaze. Patients don't usually complain of diplopia as the extraocular muscle weakness is symmetrical.

Affected patients also usually suffer from pigmentary retinopathy, which causes atrophy of the retinal pigment with bony spicule formation typical of retinitis pigmentosa. As the changes progress, patients often complain of tunnel-vision and night blindness.

Cardiac conduction defects usually develop after the onset of ophthalmoplegia and sudden death may occur as a result. Regular cardiac follow-up is essential. Other abnormalities include cerebellar ataxia, sensorineural deafness, muscle weakness and diabetes mellitus.

## Retinitis pigmentosa

Retinitis pigmentosa primarily affects the peripheral retina resulting in tunnel vision

Features

- night blindness is often the initial sign
- tunnel vision due to loss of the peripheral retina (occasionally referred to as funnel vision)
- fundoscopy: black bone spicule-shaped pigmentation in the peripheral retina, mottling of the retinal pigment epithelium

#### Associated diseases

- Refsum disease: cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome
- Alport's syndrome

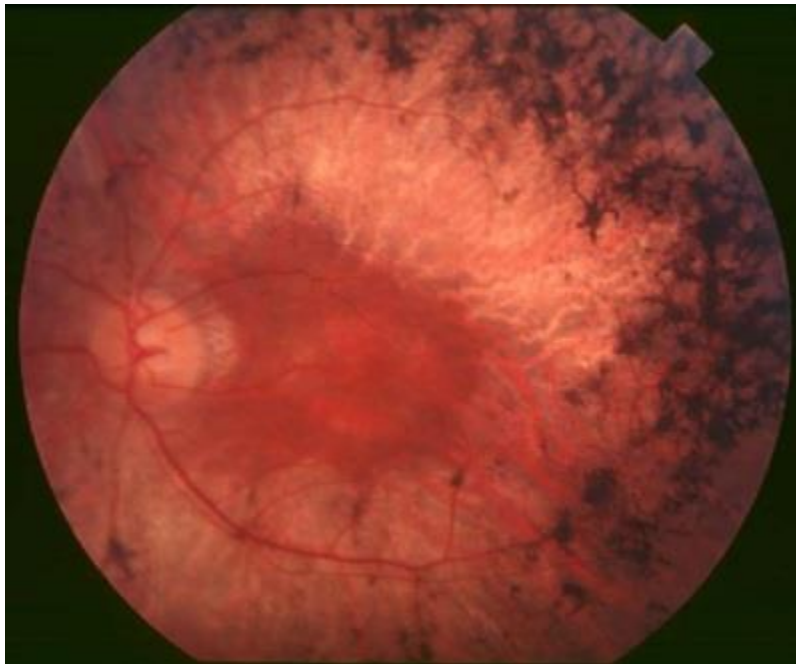


Image sourced from [Wikipedia](#)



Fundus showing changes secondary to retinitis pigmentosa

A 56-year-old female was admitted to the Emergency Department with a 90-minute history of new onset weakness in her left arm and leg. She stated that she was out shopping when the weakness suddenly came on. Since the onset of the weakness she has noticed some regained strength but still felt definite weakness. She had a past medical history comprising new atrial fibrillation for which she was undergoing investigation, hypertension, hypercholesterolaemia and asthma. She also had a perforated gastric ulcer 16 years ago. She was prescribed amlodipine 5mg OD, bisoprolol 2.5mg OD, atorvastatin 20mg OD, Clenil modulite 200mcg BD and aspirin 75mg OD. She declined formal anticoagulation regarding her atrial fibrillation. When questioned specifically, she denied the presence of any visual loss, headache, vomiting, loss of consciousness or cardiac symptoms. She smoked 20 cigarettes per day and did not consume alcohol.

On examination she was alert and walking with a hemiplegic gait. Her blood pressure was 168/74 mmHg, heart rate 78bpm, respiratory rate of 18/min, temperature of 37.2 C and oxygen saturations of 99% on air. Other than an irregularly irregular pulse, examination of the cardiovascular, respiratory and gastrointestinal systems were unremarkable.

Examination of the central neurological system revealed normal cranial nerves 2-12, with equal and reactive pupils, normal fundoscopy and a GCS of 15. Examination of the peripheral nervous system revealed the presence of power 3/5 in all muscles of the left upper and lower limbs, with decreased tone and absent deep reflexes. Power was otherwise 5/5 in all other muscle groups, with downgoing plantar reflexes. Sensation and coordination testing was unremarkable.

Initial investigations revealed the following results:

Hb 179 g/l  
MCV 99 fl  
Platelets  $452 \times 10^9/l$   
WBC  $12.2 \times 10^9/l$

ECG: atrial fibrillation 74 bpm no acute changes

CT head scan: no evidence of intracranial haemorrhage, mass shift or space occupying lesions

What is the next best management step?

[Commence intravenous heparin5%Commence thrombolysis therapy52%Arrange urgent haematology consult10%Commence aspirin 300mg and admit to stroke unit28%Commence immediate amlodipine 5mg OD 5%](#)

This lady has suffered an ischaemic stroke and fulfils the criteria for urgent thrombolysis. There are no absolute contraindications to thrombolysis and this will maximize the probability of regaining full function of the affected limbs. The other management options may serve a role but in the hyperacute setting of the above options initiating thrombolysis is the most appropriate management option.

## Stroke: management

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is  $> 3.5$  mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

<b>Absolute</b>	<b>Relative</b>
<ul style="list-style-type: none"><li>- Previous intracranial haemorrhage</li><li>- Seizure at onset of stroke</li><li>- Intracranial neoplasm</li><li>- Suspected subarachnoid haemorrhage</li><li>- Stroke or traumatic brain injury in preceding 3 months</li></ul>	<ul style="list-style-type: none"><li>- Concurrent anticoagulation (INR <math>&gt;1.7</math>)</li><li>- Haemorrhagic diathesis</li><li>- Active diabetic haemorrhagic retinopathy</li><li>- Suspected intracardiac thrombus</li><li>- Major surgery / trauma in preceding 2 weeks</li></ul>

### **Absolute**

- Lumbar puncture in preceding 7 days
- Gastrointestinal haemorrhage in preceding 3 weeks
- Active bleeding
- Pregnancy
- Oesophageal varices
- Uncontrolled hypertension >200/120mmHg

### **Relative**

## **Secondary prevention**

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

Question 4 of 174

A 45 year-old man is referred to the nephrologists for investigation of chronic kidney disease. He has a past medical history of hypertension, type 2 diabetes, and Parkinsons disease, and his medication

comprises ramipril, metformin, and bromocriptine.

Review of blood tests shows that the glomerular filtration rate (GFR) has steadily fallen from 85 to 44ml/min/1.73m<sup>2</sup> over the last year.

On questioning, his only symptom is chronic back pain which has been getting worse over the last year. On examination, both kidneys are easily palpable.

Routine investigations are as follows:

Hb	12.1 g/dl
MCV	94.2 fl
Platelets	264 x10 <sup>9</sup> /l
WCC	7.1 x10 <sup>9</sup> /l
Na	137mmol/l
K	4.6 mmol/l
Urea	13.8 mmol/l
Creatinine	157 mol/l
eGFR	44 ml/min/1.73m <sup>2</sup>
ALT	24 IU/l
ALP	78 IU/l
Bilirubin	6 mol/l
Albumin	37 g/l
Total protein	64 g/l

Serum protein electrophoresis pending

Urine dipstick                      negative for blood, protein, leucocytes, and nitrites

Abdominal ultrasound shows bilateral hydronephrosis.



What is the most likely cause of his chronic kidney disease?

[Multiple myeloma](#)12%[Diabetic nephropathy](#)7%[Bladder cancer](#)8%[Retroperitoneal fibrosis](#)60%[Autosomal dominant polycystic kidney disease](#)14%

Bilateral hydronephrosis suggests that there is an obstruction to the outflow of both kidneys. This typically occurs at the bladder outlet, raising the possibility of a bladder or prostate cancer. The absence of haematuria makes bladder cancer less likely, and the absence of lower urinary tract symptoms makes prostate cancer less likely. However, if another diagnosis were not more forthcoming it would be appropriate to investigate for these conditions.

Bilateral hydronephrosis can more unusually result from obstruction of both ureters. This occurs in retroperitoneal fibrosis, where the ureters are encased in dense fibrous tissue. Back pain is a common symptom. The condition may be idiopathic, or may occur in association with an abdominal aortic aneurysm, or secondary to long-term use of ergot derived dopamine agonists such as bromocriptine, cabergoline, or pergolide.

In the context of back pain and chronic kidney disease, multiple myeloma is a distinct possibility. Serum protein electrophoresis is required to detect the presence of a paraprotein. However, subtracting total protein from albumin (64-37) suggests that the total immunoglobulin level is 27 g/L, and therefore there is unlikely to be a significant level of paraprotein. Equally, there is unlikely to be any urinary Bence Jones protein in the absence of dipstick proteinuria. Finally, one would not expect to see hydronephrosis in myeloma kidney.

The absence of proteinuria makes diabetic nephropathy less likely, and also one would not expect to see evidence of urinary tract obstruction in this condition.

At the age of 45, autosomal dominant polycystic kidney disease can be excluded by the absence of renal cysts on ultrasound.

## **Parkinson's disease: management**

NICE published guidelines in 2017 regarding the management of Parkinson's disease.

For first-line treatment:

- if the motor symptoms are affecting the patient's quality of life: levodopa
- if the motor symptoms are not affecting the patient's quality of life: dopamine agonist (non-ergot derived), levodopa or monoamine oxidase B (MAO-B) inhibitor

Whilst all drugs used to treat Parkinson's can cause a wide variety of side-effects NICE produced tables to help with decision making:

	<b>Levodopa</b>	<b>Dopamine agonists</b>	<b>MAO-B inhibitors</b>
<b>Motor symptoms</b>	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
<b>Activities of daily living</b>	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
<b>Motor complications</b>	More motor complications	Fewer motor complications	Fewer motor complications
<b>Adverse events</b>	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

\* excessive sleepiness, hallucinations and impulse control disorders

If a patient continues to have symptoms despite optimal levodopa treatment or has developed dyskinesia then NICE recommend the addition of a dopamine agonist, MAO-B inhibitor or catechol-O-methyl transferase (COMT) inhibitor as an adjunct. Again, NICE summarise the main points in terms of decision making:

	<b>Dopamine agonists</b>	<b>MAO-B inhibitors</b>	<b>COMT inhibitors</b>	<b>Amantadine</b>
<b>Motor symptoms</b>	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
<b>Activities of daily living</b>	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
<b>Off time</b>	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
<b>Adverse events</b>	Intermediate risk of	Fewer adverse	More adverse	No studies reporting

	Dopamine agonists	MAO-B inhibitors	COMT inhibitors	Amantadine
	adverse events	events	events	this outcome
<b>Hallucinations</b>	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this outcome

### Specific points regarding Parkinson's medication

NICE reminds us of the risk of acute akinesia or neuroleptic malignant syndrome if medication is not taken/absorbed (for example due to gastroenteritis) and advise against giving patients a 'drug holiday' for the same reason.

Impulse control disorders have become a significant issue in recent years. These can occur with any dopaminergic therapy but are more common with:

- dopamine agonist therapy
- a history of previous impulsive behaviours
- a history of alcohol consumption and/or smoking

If excessive daytime sleepiness develops then patients should not drive. Medication should be adjusted to control symptoms. Modafinil can be considered if alternative strategies fail.

If orthostatic hypotension develops then a medication review looking at potential causes should be done. If symptoms persist then midodrine (acts on peripheral alpha-adrenergic receptors to increase arterial resistance) can be considered.

### Further information regarding specific anti-Parkinson's medication

#### Levodopa

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- unwanted effects: dyskinesia (involuntary writhing movements), 'on-off' effect, dry mouth, anorexia, palpitations, postural hypotension, psychosis, drowsiness
- no use in neuroleptic induced parkinsonism

#### Dopamine receptor agonists

- e.g. Bromocriptine, ropinirole, cabergoline, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
- patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence
- more likely than levodopa to cause hallucinations in older patients. Nasal congestion and postural hypotension are also seen in some patients

#### MAO-B (Monoamine Oxidase-B) inhibitors

- e.g. Selegiline
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

#### Amantadine

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
- side-effects include ataxia, slurred speech, confusion, dizziness and livedo reticularis

#### COMT (Catechol-O-Methyl Transferase) inhibitors

- e.g. Entacapone, tolcapone
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
- used in conjunction with levodopa in patients with established PD

#### Antimuscarinics

- block cholinergic receptors
- now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g. procyclidine, benzotropine, trihexyphenidyl (benzhexol)

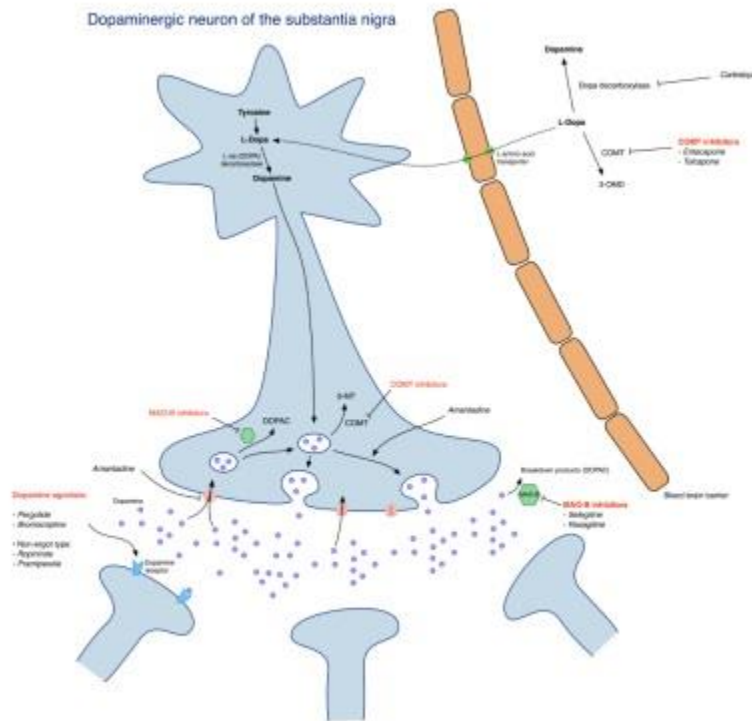


Image sourced from [Wikipedia](#)

Diagram showing the mechanism of action of Parkinson's drugs

Question 5 of 174

A 72-year-old male presents to the Parkinson's clinic with his wife, reporting increasing frequency and duration of 'off' periods. The couple finds these episodes extremely debilitating and occurs up to 11 times a day. The patient was diagnosed with Parkinson's disease 12 years ago. As a relatively young patient on diagnosis, he was commenced on ropinirole, which he continued for 5 years, before being prescribed Sinemet 6 times a day and entacapone for the following 7 years. Over past 2 years, the 'off' episodes have gradually increased in frequency in addition to the development of very mild involuntary jaw movements. He is very low in mood and has presented to the emergency department with two episodes of attempted paracetamol overdoses. He would like a more effective treatment. What would you recommend?

[Deep brain stimulation 35%](#) [Subcutaneous apomorphine 35%](#) [Reintroduce ropinirole at higher doses 11%](#) [Palliative care involvement 6%](#) [Trihexyl 13%](#)

The treatment of 'off' symptoms is particularly important in patients who have been diagnosed with Parkinson's disease for a long time. The introduction of ropinirole would not help off periods. Trihexyl is an anti-cholinergic therapy for PD patients where tremor is the predominant symptom. In the context of suicidal behaviour, the patient would not be a candidate for deep brain stimulation, which for unknown reasons, increases the risk of suicide. Subcutaneous apomorphine is a reasonable option, administered as an infusion after a test bolus, which can be used to alleviate but not cure off symptoms.

#### Question 6 of 174

An 85 year old woman was referred by her General Practitioner to the stroke team on an urgent outpatient basis after her rest home staff reported a unusual episode the previous week. The patient normally suffered from mild dementia but was independent with activities of daily life with minimal assistance from care staff. One week previously, she had been found unusually drowsy in an armchair at her home. Staff recalled that she had been inconsistent with following commands and in particular was unable to raise her left arm in the air and was unable to stand. The drowsiness and arm weakness had resolved within 30 minutes, however the patient had subsequently been more confused than normal with reduced mobility. On direct questioning, rest home staff than a few days prior to the above episode the patient had lost her balance and had sat down heavily on the ground. The care worker with her at the time was certain that the patient had not hit her head during this incident.

Past medical history included mild dementia, myocardial infarction and atrial fibrillation. Regular medications included aspirin 75 mg daily, ramipril 2.5 mg daily, bisoprolol 2.5 mg daily, simvastatin 20 mg daily and warfarin (target INR 2-3). Review of recent blood test monitoring showed that the patients INR had been well controlled over recent months with no results outside of the therapeutic range. The patient did not drink and was a long-term ex-smoker. As mentioned above, the patient normally needed minimal assistance with self-care and was fully continent.

Examination in clinic demonstrated a significant cognitive impairment (abbreviated mental test score 4/10) but without evidence of dysphasia. Pupils were equal and reactive to light with no papilloedema on fundoscopy. There was a full range of conjugate eye movements. No facial weakness or sensory loss was demonstrated. Tongue and palate function was unremarkable with no weakness of trapezius muscle. Examination of the peripheral nerves was unremarkable except for possible slight pronator drift in the left arm and an up going left plantar response. Cardiovascular examination was unremarkable except for an irregular pulse. Respiratory and abdominal examination was unremarkable.

Results of investigations performed at the time of clinic assessment are given below.

Electrocardiogram: atrial fibrillation at rate 80 bpm, normal axis, inferior T wave inversion

Chest x-ray: clear lung fields

Carotid doppler: no significant stenosis in right internal carotid artery; 50 % stenosis in left internal carotid

Transthoracic echocardiogram: mild left ventricular systolic impairment, normal valvular function, no mural thrombus

What is most likely finding on CT brain scan performed after clinic review?

[Sub-arachnoid haemorrhage6% Cerebral infarction23% Intracerebral haemorrhage8% Normal pressure hydrocephalus15% Sub-dural haematoma48%](#)

The diagnosis of sub-dural haematoma can be challenging, especially in those individuals with underlying dementia. In particular, a high index of suspicion is required in elderly patients treated with anti-coagulant drugs. Sub-dural haemorrhage commonly occurs after minor injury, with up to 50 % of cases preceded by a fall without head injury. Transient focal neurological deficit can occur in up to 20 % of cases, leading to potential for diagnostic confusion with transient ischaemic attack.

In this case the patients history of a fall, anticoagulation and worsening confusion all point towards sub-dural haematoma as the most likely underlying pathology. The lack of risk factors for cerebral infarction other than appropriately treated atrial fibrillation make this less likely. The history is less likely to be consistent with the other possible answers.

Teale E, Lliffe S, Young J. Subdural haematoma in the elderly. BMJ 2014;348:g1682.

## **Subdural haemorrhage**

### **Basics**

- most commonly secondary to trauma e.g. old person/alcohol falling over
- initial injury may be minor and is often forgotten
- caused by bleeding from damaged bridging veins between cortex and venous sinuses

### **Features**

- headache
- classically fluctuating conscious level
- raised ICP

## Treatment

- needs neurosurgical review ? burr hole

### Question 1 of 168

A 32-year-old male presents to clinic with shooting pain down both legs for one week and a mildly weak right hand. He does not recall ever having any other remarkable neurological symptoms and has not been diagnosed with any chronic medical illnesses.

He is right handed, and on examination, he has reduced fine motor control in the right hand with a brisk brachioradialis reflex on the right side. He also has subjective sensory disturbance over his trunk, but no objective sensory loss.

You suspect multiple sclerosis (MS), which findings are required to make the diagnosis of relapsing remitting MS?

[A gadolinium enhancing lesion on MRI in a typical region for MS](#)10%[At least 2 separate MRI lesions typical of MS that are of different ages \(i.e 1 enhancing and 1 not\)](#)62%[Oligoclonal bands in CSF](#)7%[Optic neuritis on examination and abnormal visual evoked potentials](#)6%[Observe the patient and await a second clinical episode before a diagnosis can be made](#)16%

McDonald's criteria are MRI criteria used in the diagnosis of multiple sclerosis. Introduced in 2001, revised in 2005 and again recently in 2010. The latest revision improves sensitivity from 46-74% with a slight trade-off in specificity (slight deterioration from 94-92%)

The diagnosis of multiple sclerosis requires establishing disease disseminated in both space and time.

Dissemination in space:

Dissemination in space requires at least 1 T2 bright lesion in two or more of the following locations:

- periventricular
- juxtacortical
- infratentorial
- spinal cord

Dissemination in time:



Dissemination in time can be established in one of two ways:

- i) A new lesion when compared to a previous scan (irrespective of timing)
  - T2 bright lesion and/or gadolinium-enhancing lesion
- ii) Presence of an asymptomatic enhancing lesion and a non-enhancing T2 bright lesion on any one scan (i.e 2 lesions of differing ages that satisfy the dissemination in space criteria)

## **Multiple sclerosis: investigation**

Diagnosis requires demonstration of lesions disseminated in time and space

### **MRI**

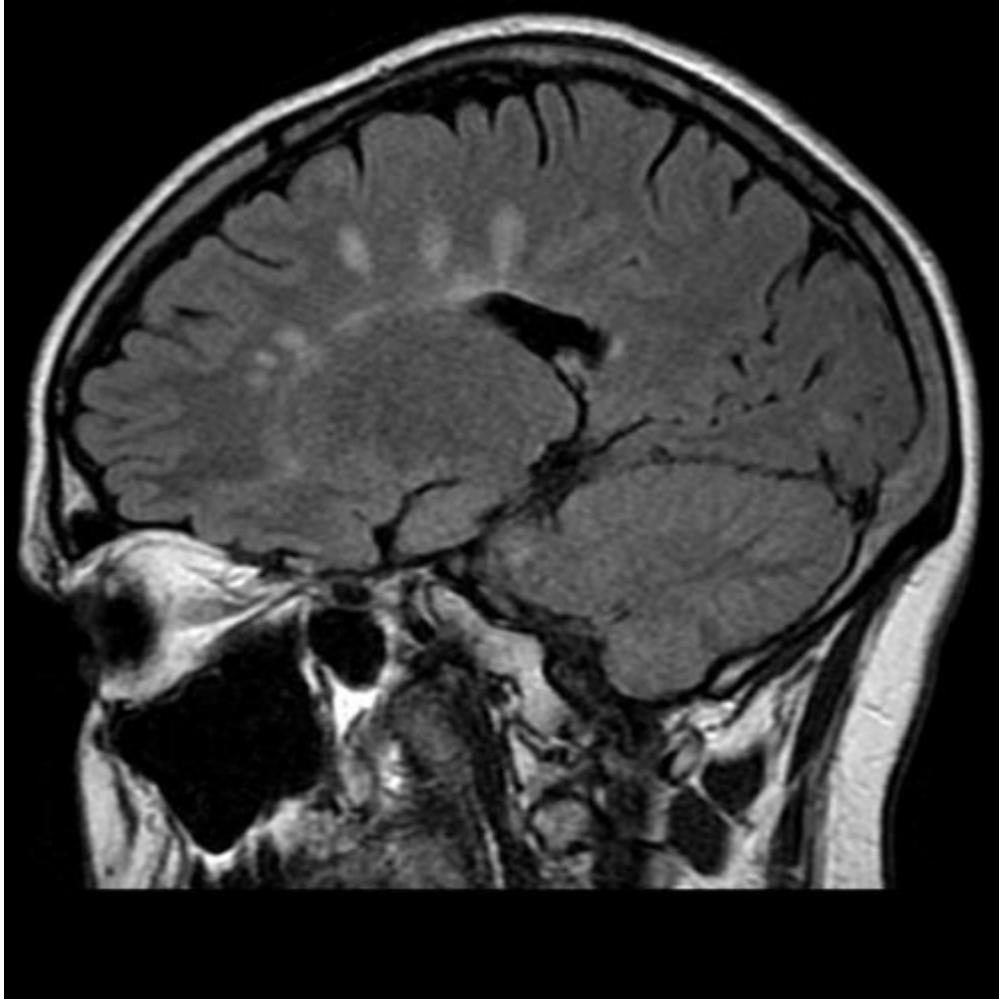
- high signal T2 lesions
- periventricular plaques
- Dawson fingers: often seen on FLAIR images - hyperintense lesions perpendicular to the corpus callosum

### **CSF**

- oligoclonal bands (and not in serum)
- increased intrathecal synthesis of IgG

### **Visual evoked potentials**

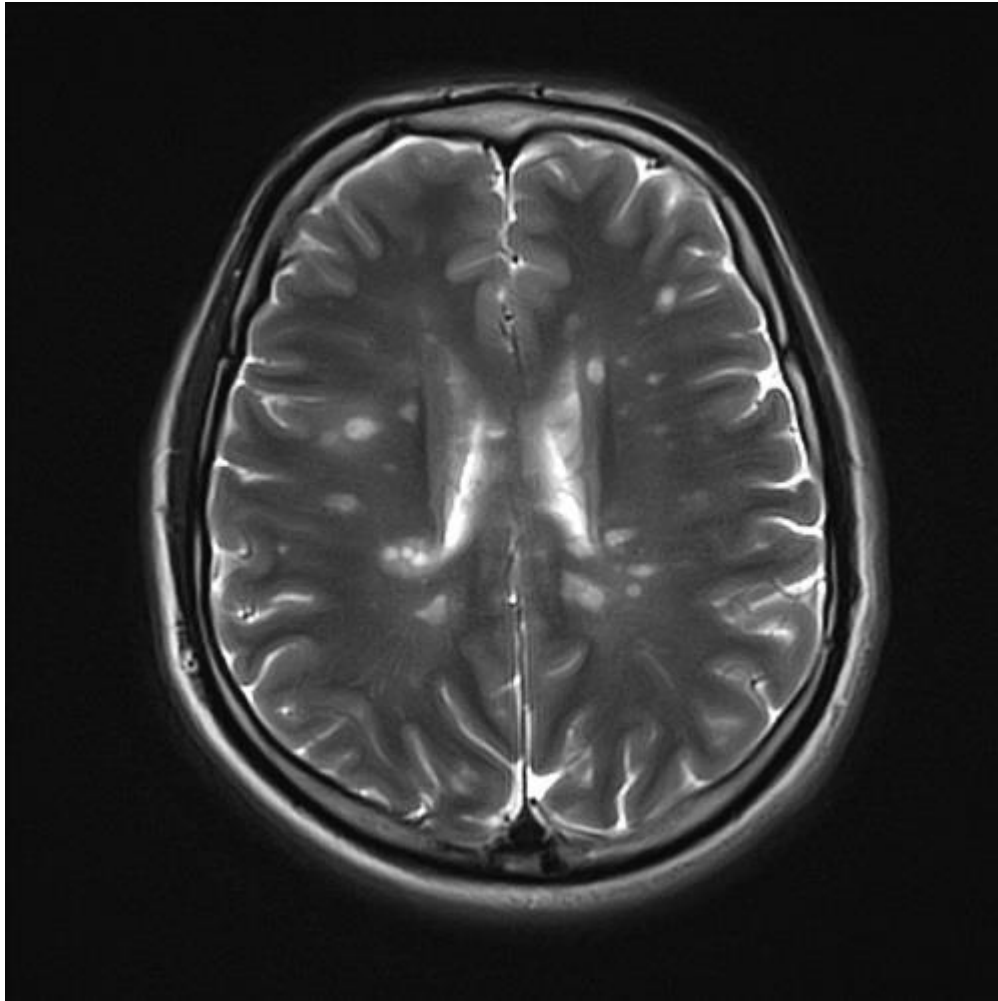
- delayed, but well preserved waveform



© Image used on license from [Radiopaedia](#)



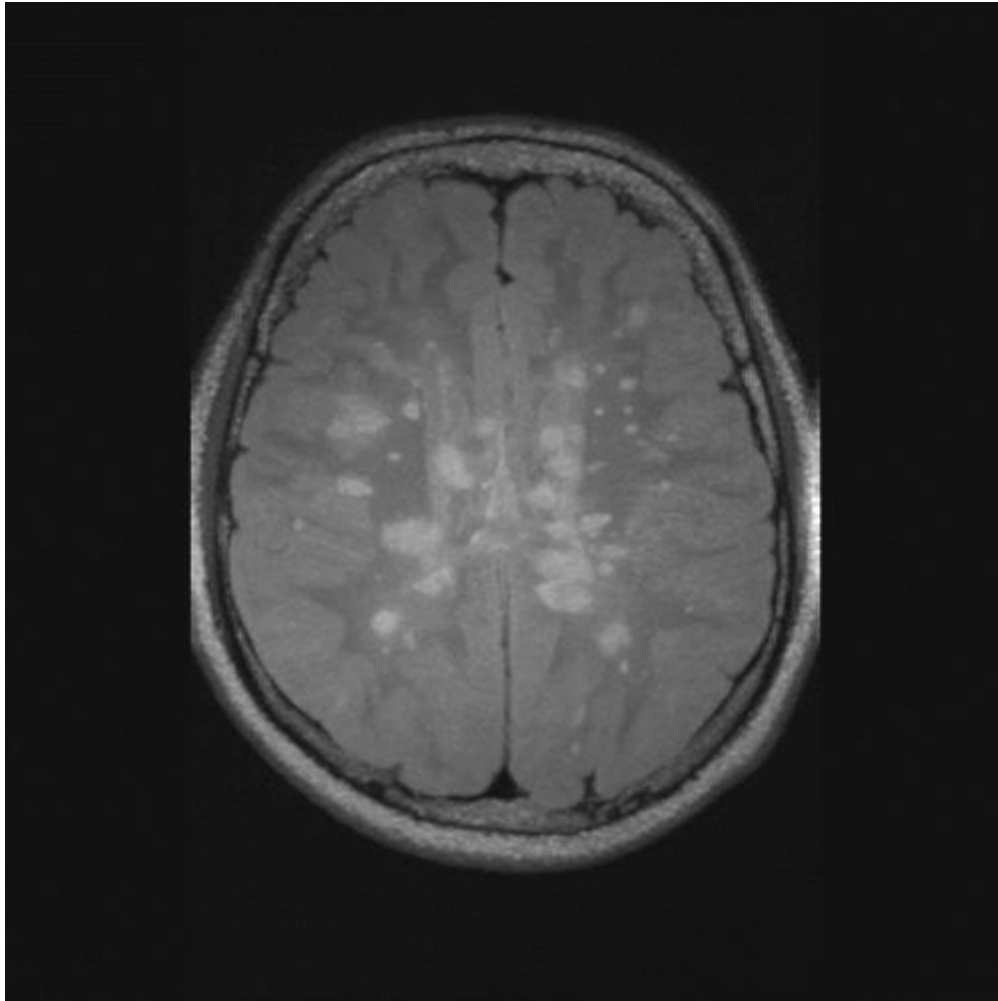
MRI showing multiple white matter plaques penpendicular to the corpus callosum giving the appearance of Dawson fingers



© Image used on license from [Radiopaedia](#)



MRI from a young patient with multiple sclerosis. Widespread periventricular, juxtacortical, post fossa and upper cervical cord high T2 regions are noted. Note the difference in the lesions with varying degrees of contrast enhancement and restricted diffusion indicating active/recent demyelination. This satisfies the diagnostic criteria in terms of separation in terms of time space.



© Image used on license from [Radiopaedia](#)



MRI FLAIR from the same patient as above. The numerous lesions are more easily identified than in the above T2 image.

#### Question 2 of 168

A 22-year-old male is referred to clinic by his GP. His initial complaint had been that his friends have been increasingly remarking on how his eyelids look increasing 'droopy' over the past 9 months. He denies any diplopia or muscle weakness. He has no past medical history, is a non-smoker and non-drinker. On examination, you note bilateral inability to abduct or adduct his eyes. Vertical gaze is also inconsistently impaired. His upper and lower limb neurological investigation was unremarkable except very mild finger-nose dysmetria, his bloods tests show no

abnormalities. His ECG demonstrates sinus rhythm with a PR interval of 260ms. Fundoscopy reveals a pigmented retina. What is the diagnosis?

[Myasthenia gravis5%Thyroid eye disease4%Oculopharyngeal musculodystrophy6%Extraocular muscle fibrosis4%Kearns-Sayre syndrome81%](#)

This young patient demonstrates a combination of retinitis pigmentosa, chronic progressive external ophthalmoplegia, bilateral ptosis, mild cerebellar signs and a cardiac conductive defect (first degree heart block). These features are consistent with a mitochondrial disorder, in particular Kearns-Sayre syndrome. Some patient may also display proximal myopathy, cognitive impairment or short stature. The underlying cause is a genetic mitochondrial disorder. Patients rarely live beyond their 40s and there are no therapeutics currently available.

## **Mitochondrial diseases**

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally encode rare neurological diseases
- poor genotype:phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

## **Histology**

- muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples include:

- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes

- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

### Question 3 of 168

A 76-year-old right-handed female presents with sudden onset flaccid right upper and lower paralysis with complete dysphasia. Her daughter reports her to have been well two hours ago.

On examination, the patients score 0/5 on her right upper and lower limb, at least 4/5 on both left limbs (examination was difficult due to her dysphasia), with a loud carotid bruit. She is also now in atrial fibrillation, a new diagnosis for her. She is well known to the stroke team: 6 weeks ago, she was admitted with a right middle cerebral artery ischaemic stroke, leaving her with minimal residual weakness on her discharge.

During her admission, she was found to have 85% carotid stenosis in her right internal carotid artery and 75% in her left internal carotid artery, for which she declined surgery. Her other past medical history includes hypertension, type 2 diabetes mellitus and dyslipidaemia. She does not take any anticoagulants. A CT head demonstrates a hypodensity in the left middle cerebral artery area distribution, consistent with an acute ischaemic stroke with no areas of haemorrhagic transformation.

What is the most appropriate next course of action?

[Intravenous alteplase33%](#)[Clopidogrel 75mg9%](#)[Aspirin 300mg47%](#)[Treatment dose low molecular weight heparin6%](#)[Warfarin5%](#)

This patient has clearly had a new ischaemic stroke. Her NIHSS score and presentation within 4.5 hours would be sufficient to warrant consideration of thrombolysis. However, the key here is to identify the contraindication to thrombolysis: refusing carotid surgery recently is NOT a contraindication. However, a recent stroke or head trauma within 3 months is. The appropriate management would be to load the patient with 300mg aspirin. Clopidogrel 75mg is preferred 14 days after an ischaemic stroke. Anticoagulation is typically started 14 days after the acute stroke, possibly sooner in patients with small infarct sizes and hence a low risk of haemorrhagic transformation.

### Stroke: management

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is  $> 3.5$  mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

Absolute	Relative
<ul style="list-style-type: none"><li>- Previous intracranial haemorrhage</li><li>- Seizure at onset of stroke</li><li>- Intracranial neoplasm</li><li>- Suspected subarachnoid haemorrhage</li><li>- Stroke or traumatic brain injury in preceding 3 months</li><li>- Lumbar puncture in preceding 7 days</li><li>- Gastrointestinal haemorrhage in preceding 3 weeks</li><li>- Active bleeding</li><li>- Pregnancy</li><li>- Oesophageal varices</li></ul>	<ul style="list-style-type: none"><li>- Concurrent anticoagulation (INR <math>&gt; 1.7</math>)</li><li>- Haemorrhagic diathesis</li><li>- Active diabetic haemorrhagic retinopathy</li><li>- Suspected intracardiac thrombus</li><li>- Major surgery / trauma in preceding 2 weeks</li></ul>

### **Absolute**

### **Relative**

- Uncontrolled hypertension >200/120mmHg

### **Secondary prevention**

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

### **Question 4 of 168**

A 45-year-old male presents with ascending weakness. He first noticed that he was tripping over more easily, but now has trouble getting out of a chair. He feels otherwise well. Of note, he did have moderate diarrhoea which had completely resolved a week prior to developing this weakness.

On examination, he is haemodynamically stable with a heart rate of 68 beats per minute and a blood pressure of 135/80 mmHg. His respiratory rate is 18 breaths per minute. He has reduced power in ankle plantar and dorsiflexion bilaterally, absent ankle jerks and reduced knee jerks.



His plantar responses are downwards.

Acutely, which of the following results will most assist you with a diagnosis?

[MRI showing inflammation of the lumbo-sacral spinal cord](#)8%[Elevated white cell count on cerebrospinal fluid \(CSF\) analysis](#)7%[Abnormal nerve conduction tests of the lower limbs](#)26%[Elevated CSF protein](#)53%[Raised erythrocyte sedimentation rate \(ESR\)](#)5%

Acutely, an elevated CSF protein level may be the only indication of an inflammatory aetiology, highly suggestive of Guillain-Barré Syndrome (GBS) or Acute Inflammatory Demyelinating Polyradiculoneuropathy in this clinical setting. The CSF white cell count is not elevated in GBS.

In relation to nerve conduction studies, these often provide normal results within the acute setting and the classic demyelination findings may not be detectable for at least a week.

### **Guillain-Barre syndrome: features**

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*).

The characteristic features of Guillain-Barre syndrome is progressive weakness of all four limbs. The weakness is classically ascending i.e. the lower extremities are affected first, however it tends to affect proximal muscles earlier than the distal ones. Sensory symptoms tend to be mild (e.g. distal paraesthesia) with very few sensory signs. Some patients experience back pain in the initial stages of the illness

#### **Other features**

- areflexia
- cranial nerve involvement e.g. diplopia
- autonomic involvement: e.g. urinary retention

#### **Less common findings**

- papilloedema: thought to be secondary to reduced CSF resorption

### Question 3 of 164

A 29-year-old man has developed a gradual onset of bilateral leg weakness over the last 24 months such that he now needs to walk with crutches. He is also intermittently incontinent of urine. He will also often fall over in the dark because he feels his balance is worse then. He has never noticed any other symptoms prior to these. He has no significant past medical conditions. He works as an accountant. He went travelling for some years in his early 20's to the Carribean, Japan and Africa. He admits occasional intravenous drug use whilst travelling and getting a tattoo. He also has casual sexual contact with sex workers occasionally whilst travelling and does not recall using barrier contraception. On examination, you find hyperreflexia bilaterally in the legs with upgoing plantar responses. He has loss of vibration and joint position sense in the legs. Legs are 3/5 power in the knee and plantar extensors and 4/5 in the flexors. He has a stomping gait. Routine blood tests plus HIV screening come back unremarkable. MRI brain and whole spine show areas of demyelination in the lumbar spine. Which test would you do to confirm the most likely suspected cause of his symptoms?

[Serm JC virus levels14%](#)[Serum and CSF HTLV-1 antibody levels31%](#)[Syphilis serology38%](#)[Hepatitis B serology4%](#)[Paired serum and cerebrospinal fluid \(CSF\) oligoclonal band levels12%](#)

The diagnosis is tropical spastic paraparesis (TSP).

This is otherwise called HTLV-1 Associated Myelopathy (HAM), describing how this demyelinating condition is caused by infection with HTLV-1. HTLV-I is a retrovirus endemic in southern Japan, equatorial Africa and South America. Transmission occurs through sexual or other intimate contacts, intrauterine, breastfeeding, sharing of needles by drug users, or blood transfusion from infected persons. This patient has many of these risk factors from his time travelling.

The incubation period between infection and symptomatic disease may be a few months up to decades and actually, the majority of infected individuals remain lifelong asymptomatic carriers. It is not clear what determines whether or not one becomes symptomatic but the key is suspected to be bigger viral loads resulting in progression to symptoms.

The presentation is with progressive upper motor neurone symptoms and signs particularly confined to the lower limbs (see below for differentials of such a presentation).

The key to knowing which of these differentials is the likely cause here is understanding the risk factors and ordering the correct tests (e.g. not missing out an HIV test); as the signs and symptoms are fairly similar in all of these upper motor neurone conditions.

### Spastic paraparesis

Spastic paraparesis describes a upper motor neuron pattern of weakness in the lower limbs

#### Causes

- demyelination e.g. multiple sclerosis
- cord compression: trauma, tumour
- parasagittal meningioma
- tropical spastic paraparesis
- transverse myelitis e.g. HIV
- syringomyelia
- hereditary spastic paraplegia
- osteoarthritis of the cervical spine

#### Question 4 of 164

A 42-year-old man presented with a partial left Horner's syndrome (ptosis with miosis, no anhidrosis), ipsilateral neck pain and reduced visual acuity on the same side.

He reported that the first symptom was neck pain and that his vision worsened over the next two hours. On admission, his blood pressure was 145/80 mmHg and heart rate was 80 beats per minute in sinus rhythm. His chest was clear.

His initial non-contrast enhanced CT brain scan showed a very small area of gliosis in the left frontal area possibly related to a distant injury, but no acute pathology.

Which of the following tests is likely to give you a diagnosis?

[MRI of the brain9%](#)[CT carotid angiogram59%](#)[Chest X-Ray9%](#)[Erythrocyte sedimentation rate \(ESR\) and temporal artery biopsy6%](#)[CT venogram of the neck and brain18%](#)

The oculosympathetic pathway leads a course from the posterior hypothalamus, through the brainstem followed by the spinal cord, over the apex of the lung to the superior cervical ganglion, and then finally ascends along with the internal carotid artery to ultimately reach the pupillary dilator muscle and Mueller's muscle of the lid. These post ganglionic fibres within the carotid sheath are vulnerable to the compressive effects of a mural haematoma or pseudoaneurysm resulting from a carotid artery dissection. Such compression can result in a partial Horner's syndrome.

In addition to this, patients with both carotid and vertebral artery dissections often present with neck pain.

Finally, in patients with a carotid dissection retinal ischaemia is often as a result of thrombi

produced within the dissected portion of the vessel that then embolize distally towards the brain or in this case, the ophthalmic artery, a branch of the internal carotid artery.

The investigation of choice to diagnose a carotid dissection is a CT carotid angiogram, however, other such as MR angiograms of the neck are also adequate.

## **Horner's syndrome**

### Features

- miosis (small pupil)
- ptosis
- enophthalmos\* (sunken eye)
- anhidrosis (loss of sweating one side)

### Distinguishing between causes

- heterochromia (difference in iris colour) is seen in congenital Horner's
- anhidrosis: see below

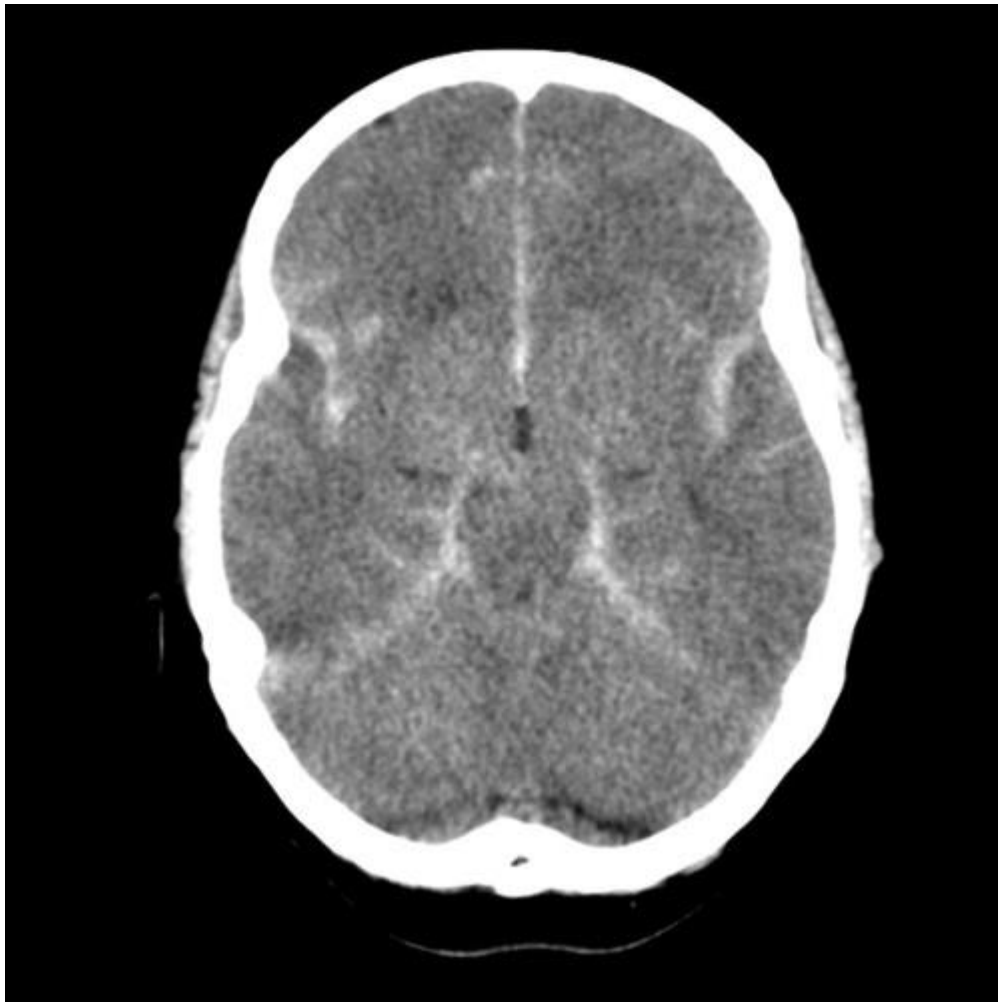
<b>Central lesions</b>	<b>Pre-ganglionic lesions</b>	<b>Post-ganglionic lesions</b>
Anhidrosis of the face, arm and trunk	Anhidrosis of the face	No anhidrosis
Stroke	Pancoast's tumour	Carotid artery dissection
Syringomyelia	Thyroidectomy	Carotid aneurysm
Multiple sclerosis	Trauma	Cavernous sinus thrombosis
Tumour	Cervical rib	Cluster headache
Encephalitis		

\*in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos

A 79-year-old woman is admitted to the Emergency Department via an ambulance after being found in an unresponsive, drowsy state. Her daughter phoned her earlier in the day routinely. At this point she complained of a headache. Upon arriving at her mother's house she found her confused and lying on the floor.

On examination her GCS is 9/15 (M4V3E2), pulse 96/min and blood pressure 140/78 mmHg.

A CT head is arranged:



© Image used on license from [Radiopaedia](#)



What is the most likely diagnosis?

[Epidural haematoma](#)6%[Subdural haematoma](#)7%[Subarachnoid haemorrhage](#)66%[Sagittal sinus thrombosis](#)11%[Cavernous sinus thrombosis](#)10%

The CT shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the

inter-hemispheric fissure. This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.

## **Subarachnoid haemorrhage**

### **Causes**

- 85% are due to rupture of berry aneurysms (conditions associated with berry aneurysms include adult polycystic kidney disease, Ehlers-Danlos syndrome and coarctation of the aorta)
- AV malformations
- trauma
- tumours

### **Investigations**

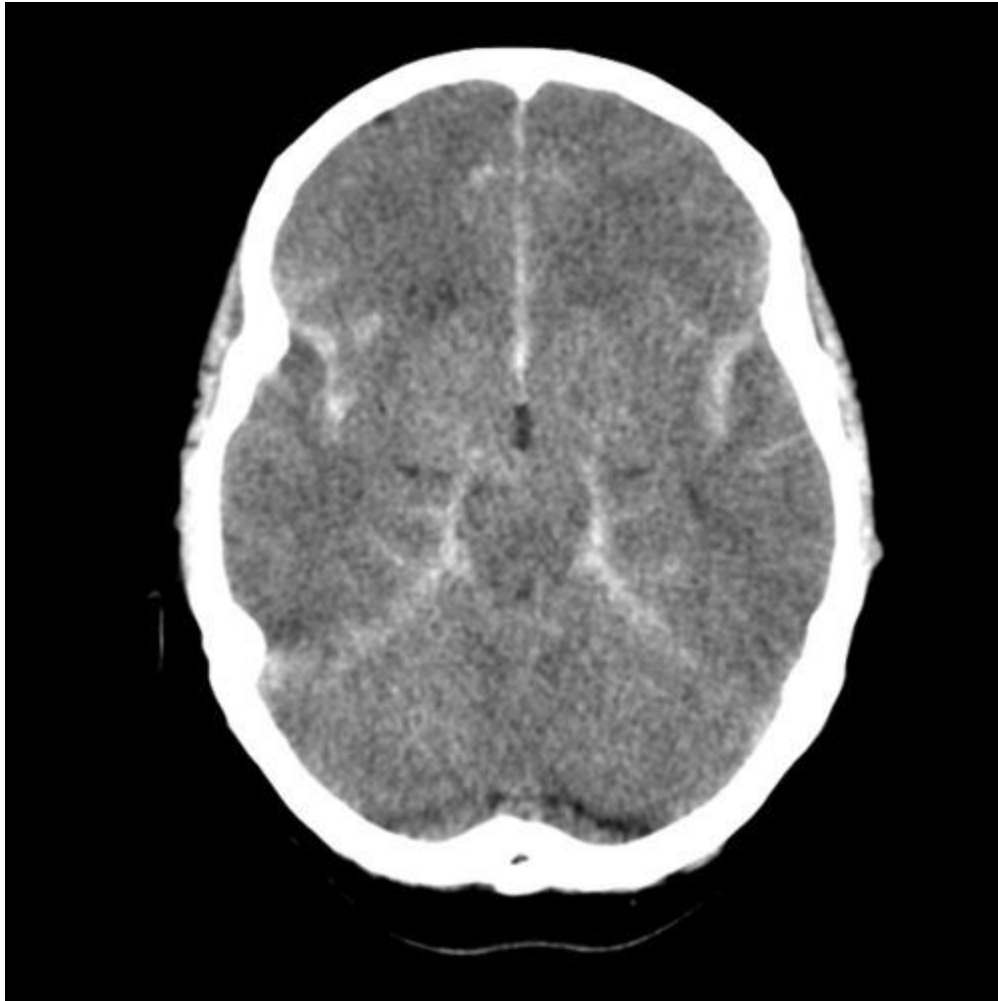
- CT: negative in 5%
- lumbar puncture: done after 12 hrs (allowing time for xanthochromia to develop)

### **Complications**

- rebleeding (in 30%)
- obstructive hydrocephalus (due to blood in ventricles)
- vasospasm leading to cerebral ischaemia

### **Management**

- neurosurgical opinion: no clear evidence over early surgical intervention against delayed intervention
- post-operative nimodipine (e.g. 60mg / 4 hrly, if BP allows) has been shown to reduce the severity of neurological deficits but doesn't reduce rebleeding\*



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CT image shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the inter-hemispheric fissure. This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.

\*the way nimodipine works in subarachnoid haemorrhage is not fully understood. It has been previously postulated that it reduces cerebral vasospasm (hence maintaining cerebral perfusion) but this has not been demonstrated in studies

A 72-year-old man is referred to the oncology team after presenting to the emergency department. The patient reports progressive lower thoracic back pain over the past three weeks. The pain had now reached an intensity that had prevented him from sleeping during the past two nights, despite over the counter analgesics. The patient reported that coughing caused a severe exacerbation of the pain, but denied radiation of the pain. The patient had previously suffered mild lower back pain after exercise, but could recall no episodes that compared in intensity to his present symptoms.

The patient's wife reported she felt the patient had been unsteady on his feet over the past few days, and reported that he had nearly fallen on several occasions. The patient denied any history of sphincter disturbance or sensory symptoms. On direct questioning, the patient revealed that he had been troubled by a severe cough over the past two months and had also lost 7 kilograms in weight. He denied any history of fevers or night sweats.

The patient had an unremarkable past medical history and took no regular medications. He was a retired builder, who had stopped smoking when he took retirement seven years previously.

Peripheral nerve examination of upper limbs: normal tone, normal power, normal coordination, normal sensation, reflexes intact and symmetrical.

Peripheral nerve examination of lower limbs: tone generally increased bilaterally with 5 beats of clonus in left lower limb; power generally slightly reduced (4+/5) bilaterally, although patient limited by back pain; normal coordination; light touch sensation reduced to mid-point between symphysis pubis and umbilicus; knee and ankle jerks brisk bilaterally, plantar response up-going in left lower limb.

Respiratory examination: borderline clubbing of fingers; reduced resonance and air entry in left upper zone.

Musculoskeletal examination: point tenderness in midline of back around level of T11 / T12 vertebrae.

What is the appropriate investigation of patient's back pain?

[MRI whole-spine within 24 hours](#)53%[MRI lumbar-thoracic spine within 24 hours](#)24%[CT lumbar-thoracic spine within 24 hours](#)8%[MRI whole-spine within 7 days](#)11%[CT myelography within 7 days](#)5%

The presentation of this patient raises strong concerns about metastatic spinal cord compression as the cause for his symptoms. In the majority of cases, the condition is secondary to bony metastasis to the vertebral spine with collapse and extra-dural compression of the spinal cord.

In around 20 % of cases of metastatic spinal cord compression there is no pre-existing diagnosis of malignancy. While this is true in the case of this patient, there are several aspects of the above assessment that are highly suspicious of a primary lung cancer.

In 95 % of cases, back pain is the most common first symptom, and can be present for up to two months before other signs occur. The patient's history of progressive pain, exacerbated by coughing, and associated with midline tenderness is typical of pain secondary to a localised lesion; however, pain can also present in a radicular pattern due to nerve root compression.



The normal upper limb examination and presence of upper motor neurone signs in the lower limbs with a sensory level, would localise the lesion to the thoracic spinal cord, and correlates with the vertebral tenderness. Bladder and bowel symptoms are often a late feature of metastatic spinal cord compression, so the absence of autonomic dysfunction does not exclude the diagnosis.

United Kingdom NICE guidance is for MRI whole-spine to be performed within 24 hours in individuals with both pain and neurological symptoms suggestive of metastatic spinal cord compression. In the presence of pain without neurological symptoms, MRI whole-spine should be performed within 7 days. It is necessary to image the entire vertebral column, as multi-level involvement is present in 30-50 % of cases.

CT scanning is often used to aid surgical or radiotherapy treatment planning. CT myelography is occasionally used in individuals with contra-indications to MRI scanning.

Al-Qurainy, Collis E. Metastatic spinal cord compression: diagnosis and management. BMJ 2016;353:i2539.

## Spinal cord lesions

The diagram belows shows cross-section view of the spinal cord:

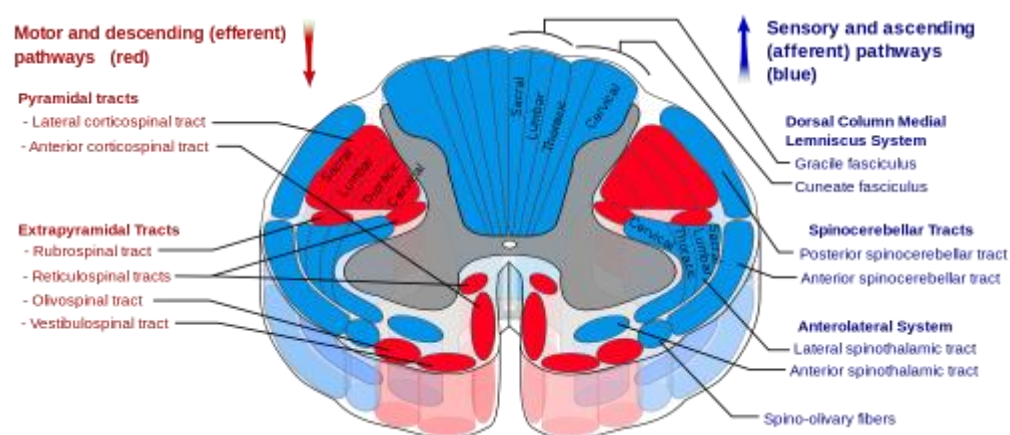


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/Spinal_cord#/media/File:Spinal_cord_cross_section.png)

## Motor lesions

Amyotrophic lateral sclerosis (motor neuron disease)

- affects both upper (corticospinal tracts) and lower motor neurons
- results in a combination of upper and lower motor neuron signs

Poliomyelitis

- affects anterior horns resulting in lower motor neuron signs

## Combined motor and sensory lesions

Disorder	Tracts affected	Clinical notes
Brown-Sequard syndrome (spinal cord hemisection)	1. Lateral corticospinal tract 2. Dorsal columns 3. Lateral spinothalamic tract	1. Ipsilateral spastic paresis below lesion 2. Ipsilateral loss of proprioception and vibration sensation 3. Contralateral loss of pain and temperature sensation
Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency)	1. Lateral corticospinal tracts 2. Dorsal columns 3. Spinocerebellar tracts	1. Bilateral spastic paresis 2. Bilateral loss of proprioception and vibration sensation 3. Bilateral limb ataxia
Friedrich's ataxia	Same as subacute combined degeneration of the spinal cord (see above)	Same as subacute combined degeneration of the spinal cord (see above)  In addition cerebellar ataxia → other features e.g. intention tremor
Anterior spinal artery occlusion	1. Lateral corticospinal tracts 2. Lateral spinothalamic tracts	1. Bilateral spastic paresis 2. Bilateral loss of pain and temperature sensation

Disorder	Tracts affected	Clinical notes
Syringomyelia	1. Ventral horns 2. Lateral spinothalamic tract	1. Flacid paresis (typically affecting the intrinsic hand muscles) 2. Loss of pain and temperature sensation
Multiple sclerosis	Asymmetrical, varying spinal tracts involved	Combination of motor, sensory and ataxia symptoms

### Sensory lesions

Disorder	Tracts affected	Clinical notes
Neurosyphilis (tabes dorsalis)	1. Dorsal columns	1. Loss of proprioception and vibration sensation

Question 3 of 160

A 78-year-old man is admitted following being found on the floor at home. He has no recollection of how he got to floor or how long he had been there. He reports feeling generally unwell and having a cough for a number of days. There is no medical history of note and he takes no regular medications. He lives alone and appears unkempt. Examination reveals bronchial breathing throughout his left mid zone. Neurologically, he has new onset weakness of left sided shoulder abduction and adduction, alongside mild weakness in left elbow flexion. Additionally, reduced sensation in the lateral aspect of his upper arm is noted. A CT head is undertaken.

CT head report      Age related involutional change. No evidence of intracranial haemorrhage or recent ischaemic event.

What is the most likely diagnosis?

[Stroke9%](#) [Rotator cuff tear10%](#) [Brachial plexus injury66%](#) [Brown-Sequard syndrome8%](#) [Botulism7%](#)

Given the pattern of neurological signs in his left limb, this would not fit with a stroke. Global weakness and sensory loss would be expected in the affected limb.

A rotator cuff tear is possible given the likely trauma. However, sensory loss would not be

expected.

Brown-Sequard syndrome is caused by damage to half of the spinal cord. It produces ipsilateral paralysis and proprioception loss, and contralateral temperature and pain loss.

Botulism classically presents with cranial nerve deficits, followed by a descending weakness and autonomic dysfunction.

A brachial plexus injury may be sustained following trauma, as in this case. The level of injury will correlate with the signs. In this patient, it is at C5, causing the specific distribution of weakness and sensory loss.

### **Brachial plexus injuries**

Erb-Duchenne paralysis

- damage to C5,6 roots
- winged scapula
- breech presentation

Klumpke's paralysis

- damage to T1
- loss of intrinsic hand muscles
- due to traction

Question 4 of 160

A 62-year-old Afro-Caribbean female is brought to the Emergency Department by husband after a 3-day history of unusual, odd behaviour at home. The family had hosted a dinner party that evening and the patient was reported to have been very disinhibited, agitated and describing hallucinations around her guests. In the past 3 weeks, she had two episodes of generalised seizures witnessed by her husband, each lasting for up to 5 minutes before spontaneously terminating, associated with urinary incontinence and tongue biting. She has no history of epilepsy and is not on any regular medications, but was diagnosed with ovarian teratoma two years ago. On examination, she has no focal neurology but you note a dystonic orofacial

movement disorder. A CT head was unremarkable, with no acute infarct, haemorrhage or space occupying lesion demonstrated.

Which investigation is most likely to produce the diagnosis?

[MRI head11%](#) [Lumbar puncture6%](#) [Anti-NMDA receptor antibodies65%](#) [Anti-MuSK antibodies8%](#) [Anti-GM1 antibodies9%](#)

The syndrome described is strongly suggestive of an autoimmune-mediated limbic encephalitis.

### **Anti-NMDA receptor encephalitis**

Anti-NMDA receptor encephalitis is a paraneoplastic syndrome, presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability. Ovarian teratomas are detected in up to half of all female adult patients, particularly prevalent in Afro-Caribbean patients<sup>1</sup>. MRI head can be normal but abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures<sup>2</sup>. CSF may demonstrate pleiocytosis but can be normal initially. Anti-MuSK is an autoantibody specific to muscle kinase in myasthenia gravis with no evidence of a thymoma and without antibodies to acetylcholine receptors. Anti-GM1 is an autoantibody specific to acute inflammatory demyelinating polyneuropathy (AIDP) variant of Guillain-Barre syndrome.

Treatment of anti-NMDA encephalitis is based of immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination. Resection of teratoma is also therapeutic.

1. Prüss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, Stoecker W, Wandinger KP. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology*. 2010;75(19):1735.
2. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091.

### **Question 6 of 160**

You are asked by nursing staff to review 78-year-old female on the ward after concerns about her blood pressure in her observations chart. Her blood pressure is 78/44mmHg, previously 120/70 mmHg 4 hours ago. You note similar hypotensive episodes yesterday and 3 days ago. At present, she is lying flat and denies any symptoms. In fact, she is awaiting discharge the next day when

her package of care can be restarted. Her medications includes: aspirin 75mg, metformin 500mg BD, Sinemet 125 TDS, bisoprolol 1.25mg. What should you do next?

[Monitor only47%](#)[Increase her dose of L-dopa16%](#)[Stop bisoprolol21%](#)[Intravenous broad spectrum antibiotics5%](#)[Intravenous fluids12%](#)

The main clue in this question is that she takes Sinemet. This is a patient who presents with a classic non-motor symptom of Parkinson's disease. A significant proportion of patients with PD demonstrate autonomic dysfunction in addition to the classic motor symptoms of rigidity, bradykinesia, resting tremor and postural instability. The patient is likely to demonstrate a significant lying/standing blood pressure difference. Blood pressure lability is a feature of dysautonomia and no action is required.

## Levodopa

### Overview

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of L-dopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- no use in neuroleptic induced parkinsonism

### Adverse effects

- dyskinesia
- 'on-off' effect
- postural hypotension
- cardiac arrhythmias
- nausea & vomiting
- psychosis
- reddish discolouration of urine upon standing

### Question 7 of 160

A 25 year old man presents to A+E in a comatose state. He was found by his university flatmate collapsed on the floor. His flatmate states that the man had been behaving bizarrely in the last 24 hours and had been quite agitated and aggressive at times. When you examine him he has a GCS

of 8 (E 2 V 1 M 5). He has a temp of 39.4°C, heart rate 120/min, blood pressure 178/89 mmHg, sats 98% on room air and respiratory rate 20/min. Chest clear abdomen soft and non-tender, bowel sounds present. Globally greatly increased tone in all 4 limbs.

When looking at his previous electronic notes the only information that you can find is a recent admission to a psychiatric hospital where a diagnosis of paranoid schizophrenia was established.

CT Brain: normal

Hb 15.4 g/dl  
Platelets  $232 \times 10^9/l$   
WBC  $11.5 \times 10^9/l$

Na<sup>+</sup> 143 mmol/l  
K<sup>+</sup> 4.1 mmol/l  
Urea 8.1 mmol/l  
Creatinine 101 µmol/l

Bilirubin 14 µmol/l  
ALP 63 u/l  
ALT 28 u/l  
Calcium 2.64 mmol/l  
Albumin 41 g/l  
Creatine kinase 21,000 iu/l  
Serum glucose 6.4 mmol/l

Lumbar Puncture:

Glucose 4.9 mmol/l  
Protein 0.3g/l  
Culture nil organisms found  
Opening pressure 21 mmHg

What is the most likely diagnosis?

[Viral meningitis5%](#)[Serotonin syndrome13%](#)[Neuroleptic malignant syndrome71%](#)[Bacterial meningitis4%](#)[Malignant hyperthermia6%](#)

The answer is neuroleptic malignant syndrome. NMS is characterised by a triad of altered conscious state, hyperpyrexia and raised CK in a person on neuroleptic medications. Young males recently started on a high dose of a high potency antipsychotic are most at risk from this potentially fatal complication. Autonomic instability is also a feature.

Serotonin syndrome shares many clinical features with NMS but normally you would expect to see GI features and cerebellar symptoms in addition and rigidity and hyperthermia are usually more mild. In addition serotonin syndrome is associated with antidepressant medication. This is therefore a less likely diagnosis in an individual recently diagnosed with schizophrenia.

Malignant hyperthermia also shares many clinical features with NMS but this is a genetic disorder provoked by the use of anaesthetic agents and there is nothing in the history to suggest this. A normal Lumbar Puncture MC+S essentially rules out bacterial meningitis and viral meningitis is unlikely to cause such severe symptoms

## **Neuroleptic malignant syndrome**

Neuroleptic malignant syndrome is a rare but dangerous condition seen in patients taking antipsychotic medication. It carries a mortality of up to 10% and can also occur with atypical antipsychotics. It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

### **Features**

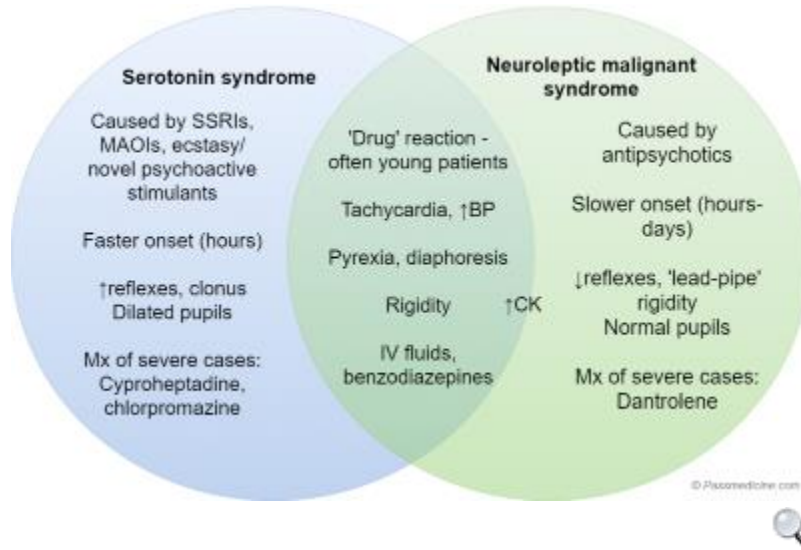
- more common in young male patients
- onset usually in first 10 days of treatment or after increasing dose
- pyrexia
- rigidity
- tachycardia

A raised creatine kinase is present in most cases. A leukocytosis may also be seen

### **Management**

- stop antipsychotic
- IV fluids to prevent renal failure
- dantrolene\* may be useful in selected cases
- bromocriptine, dopamine agonist, may also be used





Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

\*thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum

#### Question 9 of 160

A 34-year-old woman is referred to the neurology clinic for a 6 month history of progressively worsening headaches. The headaches tend to be occipital in nature and are worsened by coughing.

Neurological examination is unremarkable.

Her MRI is shown below:



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What finding is shown on the MRI?

[Brainstem cavernous angioma](#) 15% [Pituitary adenoma](#) 14% [Arnold-Chiari malformation](#) 54% [Arachnoid cyst](#) 12% [Spina bifida](#) 5%

The MRI shows herniation of the cerebellar tonsils through the foramen magnum consistent with a Chiari type I malformation.

**Arnold-Chiari malformation**

Arnold-Chiari malformation describes the downward displacement, or herniation, of the cerebellar tonsils through the foramen magnum. Malformations may be congenital or acquired through trauma.

#### Features

- non-communicating hydrocephalus may develop as a result of obstruction of cerebrospinal fluid (CSF) outflow
- headache
- syringomyelia



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MRI showing herniation of the cerebellar tonsils through the foramen magnum consistent with a Chiari I malformation

### Question 11 of 160

A 32 year old man presented to the Emergency Department with a severe headache. The headache had started suddenly that evening while the patient was at home with his girlfriend watching television. The patient described his headache as an intense throbbing pain felt all across his head. The pain had started very quickly with the patient reporting a severity of 10 / 10 within 30 seconds. The pain had eased slightly following some morphine given by the ambulance crew. The patient denied any symptoms of neck stiffness or photophobia. There were no visual symptoms and no weakness in the patient's limbs or abnormal sensation.

The patient had no previous past medical history and did not normally suffer from headaches. He took no regular medications. The patient worked as a retail assistant and lived with his girlfriend. He rarely drank alcohol but did smoke cannabis on several occasions each month. The patient's girlfriend reported that the patient had smoked cannabis that evening prior to suffering his headache.

On examination, the patient was in visible discomfort due to his headache although had no meningitic signs. Glasgow Coma Score was 15/15 and the patient was afebrile. Cranial and peripheral nerve examination was unremarkable.

Further analgesia was given to the patient and investigations requested as detailed below.

CT brain: no evidence extra-dural or sub-dural bleeding; no intracerebral haemorrhage or sub-arachnoid blood; no evidence of cerebral infarction; normal ventricular system; no radiological contra-indication to lumbar puncture

Cerebrospinal fluid results:

Red cell count	1 / mm <sup>3</sup>
White cell count	2 / mm <sup>3</sup>
Pprotein	0.75 g / L
Glucose	60 % of serum value
Microscopy	No organisms seen
Red cell breakdown products	Negative
Opening pressure	19 cmCSF

Following initial investigation as above, the patient continued to experience severe recurrent headaches similar to that experienced at presentation and was observed to have a short, generalised seizure on the admission ward prompting further investigation.

CT angiography: diffuse arterial beading identified; results otherwise as for previous CT head

What is the cause for the patient's headache?

[Atypical migraine 7%](#)[Cervical artery dissection 1%](#)[Reversible cerebrovascular vasoconstriction syndrome 59%](#)[Posterior reversible leucoencephalopathy syndrome 14%](#)[Pituitary apoplexy 9%](#)

The patient presents with a typical 'thunderclap' headache, with pain reaching a severe intensity within one minute of onset. Reversible cerebrovascular vasoconstriction syndrome (RCVS) is a cause of thunderclap headache with normal CT brain and normal or near-normal lumbar puncture results. RCVS may also be associated with focal neurological signs and seizures. Diagnosis is made by the finding of diffuse arterial beading on angiography (CT, MRI or catheter). One half of cases occur during the postpartum period or after exposure to serotonergic agents, adrenergic substances or cannabis. There are no evidence based treatments for RCVS although bed-rest and nimodipine are usually prescribed. RCVS is not always benign, with one-in-four patients suffering sub-arachnoid haemorrhage or ischaemic / haemorrhagic stroke

The alternate answers listed in the stem are all causes of thunderclap headache with normal CT brain and lumbar puncture (i.e. sub-arachnoid haemorrhage excluded). None of these conditions are associated with diffuse arterial bleeding and so are less likely differential than RCVS.

Ducros A, Boussier M. Thunderclap headache. BMJ 2012;345:e8557.

## **Thunderclap headache**

Thunderclap headache describes a sudden (reaches maximum severity within seconds to minutes of onset) and severe headache.

### **Causes**

- subarachnoid hemorrhage
- cerebral venous sinus thrombosis
- internal carotid artery dissection
- pituitary apoplexy
- reversible cerebral vasoconstriction syndrome
- primary sexual headache
- posterior reversible leucoencephalopathy syndrome

A 75-year-old man is being reviewed after transient expressive dysphasia and clumsiness in the right hand. His symptoms completely resolved after 20 minutes.

He does not have a background diagnosis of ischaemic heart disease or diabetes but is an ex-smoker with a 50 pack year history. His blood pressure was 160/70 mmHg and he was in sinus rhythm. He had no detectable neurological signs on examination.

His MRI brain scan showed a very small area of restricted diffusion in the left frontotemporal region consistent with ischaemia.

He has a total fasting cholesterol of 4 mmol/L (normal) with an LDL level of 2.5 mmol/L (normal). With regards to cholesterol, in addition to dietary advice and exercise what else may benefit this patient?

[Commence on a fibrate 5%](#)[Commence a statin 72%](#)[Commence a fibrate and a statin 5%](#)[Commence fish oil tablets5%](#)[Assess for diabetes and only if present commence a statin 12%](#)

In addition to diet and exercise modifications, all patients who are diagnosed with stroke or TIA should be commenced on statin therapy irrespective of the cholesterol level.

## **Transient ischaemic attack**

NICE issued updated guidelines relating to stroke and transient ischaemic attack (TIA) in 2008. They advocated the use of the ABCD2 prognostic score for risk stratifying patients who've had a suspected TIA:

<b>Criteria</b>	<b>Points</b>
<b>A</b> Age $\geq$ 60 years	1
<b>B</b> Blood pressure $\geq$ 140/90 mmHg	1
<b>Clinical features</b>	
<b>C</b> - Unilateral weakness	2
- Speech disturbance, no weakness	1
<b>Duration of symptoms</b>	
<b>D</b> - $>$ 60 minutes	2
- 10-59 minutes	1
Patient has diabetes	1

This gives a total score ranging from 0 to 7. People who have had a suspected TIA who are at a higher risk of stroke (that is, with an ABCD2 score of 4 or above) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment and investigation within 24 hours of onset of symptoms
- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors

If the ABCD2 risk score is 3 or below:

- specialist assessment within 1 week of symptom onset, including decision on brain imaging
- if vascular territory or pathology is uncertain, refer for brain imaging

People with crescendo TIAs (two or more episodes in a week) should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.

#### Antithrombotic therapy

- clopidogrel is recommended first-line (as for patients who've had a stroke)
- aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel
- these recommendations follow the 2012 Royal College of Physicians National clinical guideline for stroke. Please see the link for more details (section 5.5)
- these guidelines may change following the CHANCE study (NEJM 2013;369:11). This study looked at giving high-risk TIA patients aspirin + clopidogrel for the first 90 days compared to aspirin alone. 11.7% of aspirin only patients had a stroke over 90 days compared to 8.2% of dual antiplatelet patients

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\* criteria or > 50% according to NASCET\*\* criteria

\*European Carotid Surgery Trialists' Collaborative Group

\*\*North American Symptomatic Carotid Endarterectomy Trial

#### Question 1 of 145

A 77-year-old female has two episodes of weakness affecting the left arm and leg each lasting ten minutes, both within the space of 2 days. She did not attend the emergency department after

the first episode. Her only significant past medical history is hypertension, for which she takes amlodipine 5mg OD. She has experienced one similar episode to this one year ago but did not seek medical attention. Her daughter is present who informs you that the patient has lost a significant amount of weight in the last year. On further questioning, she reports some haemoptysis lately. Her blood pressure in the department was 170/90mmHg initially.

Her bloods reveal

Hb 11.5 g/dl  
Platelets  $149 \times 10^9/l$   
WBC  $13.1 \times 10^9/l$

Na<sup>+</sup> 132 mmol/l  
K<sup>+</sup> 5.3 mmol/l  
Creatinine 111  $\mu$ mol/l  
CRP 15 mg/l

ECG: Sinus tachycardia, rate 104/min

What is the most appropriate management for this lady?

[Aspirin + transient ischaemic attack \(TIA\) clinic referral15%](#)  
[Aspirin and dipyridamole + TIA clinic referral5%](#)  
[Aspirin and clopidogrel + TIA clinic referral8%](#)  
[Admit for CT head + aspirin68%](#)  
[Reassure and discharge4%](#)

This question tests the candidate's knowledge of TIA risk stratification. The patient fulfils the criteria of crescendo TIAs (two TIAs in a 7 day period). This warrants urgent assessment and urgent imaging. Any patient with an ABCD2 score greater than 4 or crescendo TIA should be admitted.

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Duration of symptoms	
<b>D</b> - > 60 minutes	2
- 10-59 minutes	1
Patient has diabetes	1

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- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled

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\*\*North American Symptomatic Carotid Endarterectomy Trial

### Question 3 of 145

A 45-year-old lady presented to the emergency department with prolonged fever and malaise, She had a new murmur and clinical signs clearly indicating subacute bacterial endocarditis. ECHO confirms vegetations on her aortic valve and blood culture is still pending. She is a known case of myasthenia gravis and has been warned against taking some groups of antibiotics.

Which of the following antibiotics can worsen the symptoms of myasthenia gravis?

[Gentamicin66%](#)[Augmentin5%](#)[Meropenem5%](#)[Benzylpenicillin7%](#)[Trimethoprim sulphamethoxazole16%](#)

Answer: Gentamicin.

Aminoglycosides are known to worsen myasthenia gravis. Other medications that have this effect include: ciprofloxacin, verapamil, beta blockers like propranolol, lithium, D-penicillamine and muscle relaxants like Botox.

Update on myasthenia gravis B R Thanvi1, T C N Lo2  
<http://pmj.bmj.com/content/80/950/690.full>

### **Myasthenia gravis: exacerbating factors**

The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of myasthenia gravis . Symptoms become more marked during the day

The following drugs may exacerbate myasthenia:

- penicillamine
- quinidine, procainamide
- beta-blockers
- lithium

- phenytoin
- antibiotics: gentamicin, macrolides, quinolones, tetracyclines

#### Question 6 of 145

A 57-year-old male presents with a 3 months history of increasing clumsiness in his hands and arms. He has a complicated past medical history: 22 years ago, he underwent a renal transplant after a progressive deterioration in his renal function following diagnosis with autosomal dominant polycystic kidney disease aged 25. His transplant has functioned well since but the patient has since undergone two resections of squamous cell carcinomas and one serious lengthy hospital admission for a systemic fungal infection. He stopped working a year ago as a wine merchant, after complaining that he was no longer able to differentiate 'the smells of his wines as he got older'.

On examination, he is alert and orientated. Questioning was challenging due to his hearing impairment, despite bilateral hearing aids. He scored 17/30 on a mini-mental examination. Pupils were reactive with a full range of eye movements. Facial power and sensation were normal, with symmetrical palatal elevation and no tongue deviation. He was profoundly deaf bilaterally. Tone, power and sensation were normal, reflexes were present with downgoing plantars. However, you note significant bilateral finger-nose dysmetria and heel-shin mal co-ordination.

Which investigation is likely to produce the unifying diagnosis?

[Lumbar puncture for cerebrospinal fluid including 14-3-3, S10025%EEG4%MRI head33%Neurogenetic testing31%Nerve conduction studies and EMG7%](#)

The patient has presented with anosmia, bilateral symmetrical ataxia, cognitive impairment and sensorineural hearing loss, classical symptoms of superficial siderosis, which would be demonstrated on MRI head, with siderosis typically prominent in the posterior fossa. The underlying cause for iron deposition is thought to be due to chronic or previous intracerebral haemorrhages. In the case of this patient, the association of polycystic kidney disease with brain aneurysms are likely to be significant. In other patients, previous neurosurgery or head trauma can similarly result in siderosis. There is no current treatment for superficial siderosis but case reports have demonstrated possible improvements with lipid-soluble iron chelators.

### **Superficial siderosis**

Superficial siderosis describes the chronic deposition of iron in neurons of the central nervous

system. The most common cause is chronic bleeding secondary to either a subarachnoid haemorrhage or subdural haemorrhage.

#### Features

- sensorineural hearing loss
- ataxia
- dementia
- anosmia
- anisocoria

#### Question 8 of 145

A 45-year-old lady was admitted to the Medical Admission Unit with a 16-hour history of weakness. Two days prior to the admission she experienced a sensation of double vision and shortly afterwards had become more unsteady when walking. The weakness developed initially in her arms and was shortly followed by weakness in her legs. Her past medical history included a history of coeliac disease for which she adhered to a strict gluten-free diet, but she was otherwise fit and well.

On examination, she was not distressed and was fully orientated to her surroundings. She had a temperature of 37.6°C, a heart rate of 88/min, a respiratory rate of 18/min and a blood pressure of 182/82 mmHg. The cardiovascular and respiratory examination was otherwise unremarkable. Examination of the abdomen revealed a mass arising from the symphysis pubis. Examination of her cranial nerves revealed a failure of bilateral external gaze, as well as diplopia on asking the patient to fixate down and in. Her pupils were dilated but reactive. Fundoscopy revealed no abnormalities, and cranial nerve examination was otherwise unremarkable. The tone was reduced in all muscle groups, with a power of grade 3/5 in all muscle groups. Reflexes were absent in all limbs and plantar responses were normal. She was unable to mobilise independently and an ataxia was noted.

Initial investigations revealed the following:

Hb	132 g/l
Platelets	$222 \times 10^9/l$
WBC	$5.8 \times 10^9/l$
ESR	16 mm/hr
Na <sup>+</sup>	139 mmol/l
K <sup>+</sup>	3.7 mmol/l
Urea	4.3 mmol/l

Creatinine 77  $\mu\text{mol/l}$   
Bilirubin 11  $\mu\text{mol/l}$   
ALP 101 u/l  
ALT 22 u/l  
Glucose 6.0 mmol/l  
CRP 22 mg/l

Appearance Clear  
Glucose 4.5 mmol/l  
Protein 0.6 g/l  
White cells 3 /  $\text{mm}^3$

CT brain scan: normal appearances, no evidence of haemorrhage, midline shift or space occupying lesion.

What is the single investigation most likely to lead to a diagnosis?

[Anti Jo1 antibodies11%Anticholinesterase antibodies12%Anti GQ1b antibodies55%Anti GM1 antibodies17%Antinuclear antibodies5%](#)

The combination of ophthalmoplegia, ataxia and areflexia is strongly suggestive of Miller-Fisher syndrome, a variant of Guillain-Barre syndrome (GBS). Anti GQ1b antibodies are present in 90% of cases. Anti GM1 antibodies are present in axonal neuropathies including GBS but also other conditions and are not specific to Miller Fisher syndrome. Anti Jo1 antibodies are found in polymyositis whilst anticholinesterase antibodies are found in myasthenia gravis.

## **Guillain-Barre syndrome**

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*)

### **Pathogenesis**

- cross reaction of antibodies with gangliosides in the peripheral nervous system
- correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated
- anti-GM1 antibodies in 25% of patients

## Miller Fisher syndrome

- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. The eye muscles are typically affected first
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- anti-GQ1b antibodies are present in 90% of cases

### Question 1 of 135

A 64 year old man presents with a 6 month history of abnormal behaviours which have been noticed by his wife. He has described seeing vivid visual hallucinations of clowns in his living room which sometimes talk to him and appear very real. He believes that he is the head of a circus and is about to go on a world tour although this is not true.

At times he is lucid and is fully independent but at other times he is disorientated in time and place and is unable to perform simple tasks such as preparing food and going to the shops. His wife thinks that his mood is also lower since the onset of symptoms. He presented in A+E today because of having a second fall in two weeks.

There is no history of infective symptoms. He went to see his GP two days ago who thought that he may have a UTI and prescribed trimethoprim.

He has a history of stroke 10 years ago and hypertension and takes warfarin, amlodipine and enalapril.

Physical examination is unremarkable except for slightly increased tone on the left side compared to the right.

Bloods:

Hb 14.9 g/dl

Platelets  $387 \times 10^9/l$

WBC  $12.8 \times 10^9/l$

Na<sup>+</sup> 142 mmol/l

K<sup>+</sup> 4.6 mmol/l

Urea 6.4 mmol/l

Creatinine 84  $\mu\text{mol/l}$

Bilirubin 6 µmol/l  
ALP 64 u/l  
ALT 15 u/l  
Calcium 2.35 mmol/l  
Albumin 41 g/l

MSU (from GP from 2 days ago): Heavy growth of E.coli Sensitive to trimethoprim, nitrofurantoin, amoxicillin and co-amoxiclav

CT Brain: some generalised atrophy and periventricular white matter changes normal for age. Changes in keeping with an old left sided lacunar infarct

Mini Mental State Examination 17/30

Which medications would most appropriately treat the underlying diagnosis?

[Olanzapine22%Rivastigmine39%Co-amoxiclav14%Sinemet18%Aspirin 300mg6%](#)

The answer is Rivastigmine. The diagnosis here is Lewy Body dementia. Lewy body dementias core clinical features are fluctuating g cognition, visual hallucinations (present in 2/3rds of cases) and parkinsonism. Two out of three are needed for diagnosis. The visual hallucinations are often very vivid. This patient definitely has two out of the three. He also may have parkinsonism as he has bilaterally increased tone that is not in keeping with his old lacunar infarct.

He also has a few supportive features of Lewy Body Dementia hallucinations in other modalities, delusions, depression and repeated falls.

Currently, evidence best supports cholinesterase inhibitors in the treating of Lewy Body Dementia. It must be remembered that these patients have high sensitivity to neuroleptics so Olanzapine should not be used here. Schizophrenia is a less likely diagnosis as visual hallucinations are rare in late onset schizophrenia and late onset schizophrenia itself is rare. Also, fluctuating mental state is not usually seen in schizophrenia.

Whilst this patient has a UTI, it is sensitive to trimethoprim and therefore is already being appropriately treated and therefore further antibiotics are not required. As the symptoms have been present for 6 months, UTI is unlikely to be the underlying diagnosis.

Whilst the patient does have risk factors for stroke and focal neurology and a TIA is possible, it does not explain his other symptoms and therefore aspirin would not therefore represent treatment for the underlying diagnosis.

The patient does show features of parkinsonism but a diagnosis of Lewy Body is more suggested by the cognitive and psychiatric symptoms and therefore Sinemet would be not be considered before a cholinesterase inhibitor.

## **Lewy body dementia**

Lewy body dementia is an increasingly recognised cause of dementia, accounting for up to 20% of cases. The characteristic pathological feature is alpha-synuclein cytoplasmic inclusions (Lewy bodies) in the substantia nigra, paralimbic and neocortical areas

The relationship between Parkinson's disease and Lewy body dementia is complicated, particularly as dementia is often seen in Parkinson's disease. Also, up to 40% of patients with Alzheimer's have Lewy bodies

Neuroleptics should be avoided in Lewy body dementia as patients are extremely sensitive and may develop irreversible parkinsonism. Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent

### **Features**

- progressive cognitive impairment
- parkinsonism
- visual hallucinations (other features such as delusions and non-visual hallucinations may also be seen)

### **Diagnosis**

- usually clinical
- single-photon emission computed tomography (SPECT) is increasingly used. It is currently commercially known as a DaTscan. Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope. The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%

### **Question 3 of 135**

A 25-year-old woman attends neurology clinic for on-going follow-up of her epilepsy. She had been diagnosed with generalised epilepsy 7 years previously, following a series of generalised tonic-clonic seizures. At the time of diagnosis, no specific cause for the patient's seizures had



been identified. Since the patient's diagnosis, she had trialled a number of treatment combinations, with good seizure control achieved around 4 years after diagnosis.

During clinic review today, the patient declared herself in good general physical health. Her epilepsy continued to be well controlled, with one seizure in the past year and none in the previous 6 months. She also discussed her plans to start a family in the coming months and wanted to know if her current treatment regime would be safe during pregnancy. The patient explained that she had been reading about the risks of epilepsy drugs in pregnancy, and would be keen to alter her treatment regime to minimise the risks to her baby, even if that meant the patient experiencing an increase in seizure frequency.

The patient's previous experience with antiepileptic medications was discussed. The patient had been settled on a regime of lamotrigine 150 mg twice daily and topiramate 200 mg twice daily for the previous 2 years, and had not experienced any significant unwanted effects during this time. At the time of her epilepsy diagnosis, she had initially been treated with lamotrigine monotherapy, which failed to provide adequate seizure control. Subsequently, levetiracetam had been trialled as an adjunctive therapy but was poorly tolerated due to gastrointestinal symptoms and anorexia. Topiramate was then trialled as an adjunctive therapy with success, with titration of doses to the levels described above.

The patient took no other regular medications and had no other known drug allergies. She reported using a Mirena coil and condoms for contraception. The patient was employed as a junior solicitor and did not smoke or take any alcohol.

What is the most appropriate strategy to minimise risk to the patient and to the fetus in any future pregnancy?

[Aim for topiramate monotherapy at lowest effective dose9%](#)[Aim for lamotrigine monotherapy at lowest effective dose44%](#)[Aim for lamotrigine and carbamazepine dual-therapy16%](#)[Continue with current medication regime25%](#)[Aim to stop all antiepileptic medications5%](#)

Family planning and pregnancy can be a time of anxiety for a woman with epilepsy and their families. An increase in seizure frequency is reported to occur in 14-32 % of pregnant women with epilepsy. Seizures can be harmful to both mother and fetus. The risk of major congenital malformation in a child born to a woman taking antiepileptic drugs is increased compared to the general population (roughly from 1-3 / 100 live births, to 2-5 / 100 live births).

There are no randomised controlled trials of antiepileptic drugs in pregnancy, with data based on observational studies only. From these trials, general conclusions have been reached:

- Valproate has the highest risk of teratogenicity, with topiramate having a moderate risk
- Lamotrigine, levetiracetam and carbamazepine are considered to have the lowest risk of teratogenicity, although carbamazepine is often poorly tolerated
- Treatment with more than one drug (polytherapy) increases the risk of teratogenicity compared to monotherapy

Therefore, in this case, the most appropriate strategy for this patient would be to aim to find a stable dose of lamotrigine monotherapy (a drug she is known have efficacy and be tolerable to her) with cessation of the potentially teratogenic topiramate. The removal of the enzyme-inducing effect of topiramate on the lowest effective dose of lamotrigine should be considered. The risk of adjustments to her medication regime reducing seizure control should be discussed with the patient, including the risk of sudden unexpected death in epilepsy.

Kinney M, Morrow J. Epilepsy in pregnancy. BMJ 2016;353:i2880.

### **Epilepsy: pregnancy and breast feeding**

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus. All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy to minimise the risk of neural tube defects. Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

#### **Other points**

- aim for monotherapy
- there is no indication to monitor antiepileptic drug levels
- sodium valproate: associated with neural tube defects
- carbamazepine: often considered the least teratogenic of the older antiepileptics
- phenytoin: associated with cleft palate
- lamotrigine: studies to date suggest the rate of congenital malformations may be low. The dose of lamotrigine may need to be increased in pregnancy

Breast feeding is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn

### **Sodium valproate**

The November 2013 issue of the Drug Safety Update also carried a warning about new evidence showing a significant risk of neurodevelopmental delay in children following maternal use of sodium valproate.

The update concludes that sodium valproate should not be used during pregnancy and in women

of childbearing age unless clearly necessary. Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.

#### Question 4 of 135

A 25-year-old female was seen in the neurology clinic with a six-year history of headaches. The headaches occur on average two to three times per week, and she described them as a one-sided pulsating headache with associated nausea and intolerance of light lasting for four-six hours before subsiding. The headaches worsened with exertion and when they occurred she would be disabled from continuing with normal daily activities, instead resorting to taking refuge in a darkened room. She denied the presence of any transient neurological deficit or facial lacrimation, and other than the associated photophobia she denied any ocular involvement. She denied the presence of weight loss or early morning headache. Her past medical history included hypothyroidism for which she was prescribed levothyroxine 125mcg OD.

Investigations conducted are as follows:

TSH 0.36 u/l

MRI: presence of normal intracranial appearances, no evidence of space occupying lesion, intracerebral haemorrhage or mass effect

She was trialled on propranolol 80mg M/R which reduced the frequency of the headaches, but unfortunately she did not tolerate the adverse effects. Which one of the following interventions is most appropriate to prevent the headaches from occurring?

[Amitriptyline 16% Gabapentin 11% Sodium valproate 7% Increase dose of levothyroxine 6% Topiramate 60%](#)

This lady is suffering from migraines without aura. The NICE guidelines suggest that she is offered either propranolol or topiramate first line as migraine prophylaxis, and as she has not tolerated propranolol the next suitable option would, therefore, be topiramate. Note that topiramate like all antiepileptics is teratogenic and she would, therefore, need to be on suitable contraception prior to commencing topiramate. Gabapentin is suggested as a second line treatment option, and amitriptyline is only suggested as a prophylaxis option if the patient is already using amitriptyline and it is providing benefit. Her TSH is already suppressed sufficiently and so increasing the dose of levothyroxine would not be appropriate.

## Migraine: management

It should be noted that as a general rule 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis. NICE produced guidelines in 2012 on the management of headache, including migraines.

### Acute treatment

- first-line: offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol
- for young people aged 12-17 years consider a nasal triptan in preference to an oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide\* or prochlorperazine and consider adding a non-oral NSAID or triptan

### Prophylaxis

- prophylaxis should be given if patients are experiencing 2 or more attacks per month. Modern treatment is effective in about 60% of patients.
- NICE advise either topiramate or propranolol 'according to the person's preference, comorbidities and risk of adverse events'. Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives
- if these measures fail NICE recommend 'a course of up to 10 sessions of acupuncture over 5-8 weeks' or gabapentin
- NICE recommend: 'Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
- for women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- pizotifen is no longer recommend. Adverse effects such as weight gain & drowsiness are common

\*caution should be exercised with young patients as acute dystonic reactions may develop

### Question 5 of 135

A 78-year-old man is brought to see you in clinic by his daughter. He has a diagnosis of Alzheimer's dementia and although currently coping well, has significantly impaired short-term

memory.

Currently, his daughter attends daily for all meals, cleaning, and shopping. He continues to live in his own home and is alone overnight. She has, however, become concerned as he continues to drive 5 miles three times a week and she is unsure if this is safe. Which of the following is the best course of action regarding his driving licence?

[He is disqualified from driving16%](#)[He is allowed to drive, but only if daughter is present9%](#)[There is no need to contact the DVLA, continue to drive9%](#)[Assess his risk factors, report to the DVLA and await advice57%](#)[He is safe if his mini mental state examination score >119%](#)

The DVLA guidance states this is a difficult decision to make. The presence of impaired short-term memory, disorientation or loss of insight suggests someone with dementia is not fit to drive.

In this case, the correct answer would be to contact the DVLA, assess the risk factors and take further advice. He should not be immediately disqualified; he warrants a more careful assessment and decision with support from the DVLA. The factors that suggest someone with dementia may not be safe to drive include significantly impaired short-term memory, poor attention and concentration, and impairment of planning.

DVLA guidance: Dementia or any organic brain syndrome.

<https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals-conditions-d-to-f>

## **DVLA: neurological disorders**

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Epilepsy/seizures - all patient must not drive and must inform the DVLA

- first unprovoked/isolated seizure: 6 months off if there are no relevant structural abnormalities on brain imaging and no definite epileptiform activity on EEG. If these conditions are not met then this is increased to 12 months
- for patients with established epilepsy or those with multiple unprovoked seizures:
  - → may qualify for a driving licence if they have been free from any seizure for 12 months
  - → if there have been no seizures for 5 years (with medication if necessary) a 'til 70 licence is usually restored
- withdrawal of epilepsy medication: should not drive whilst anti-epilepsy medication is being withdrawn and for 6 months after the last dose

## Syncope

- simple faint: no restriction
- single episode, explained and treated: 4 weeks off
- single episode, unexplained: 6 months off
- two or more episodes: 12 months off

## Other conditions

- stroke or TIA: 1 month off driving, may not need to inform DVLA if no residual neurological deficit
- multiple TIAs over short period of times: 3 months off driving and inform DVLA
- craniotomy e.g. For meningioma: 1 year off driving\*
- pituitary tumour: craniotomy: 6 months; trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- narcolepsy/cataplexy: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'
- chronic neurological disorders e.g. multiple sclerosis, motor neuron disease: DVLA should be informed, complete PK1 form (application for driving licence holders state of health)

\*if the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free

## Question 6 of 135

A 61-year-old male presenting with his 6th episode of binocular visual loss, which he describes as 'lights' and 'white dots' over the past 14 months. He denies any limb or facial weakness or sensory loss. He denies having a headache. He is an active smoker, with a 60 pack year smoking history and has known hypertension on ramipril 5mg OD. Your neurological exam is unremarkable; CT head demonstrates no acute infarct or haemorrhage. MRI head is unremarkable. What is the most likely diagnosis?

[Posterior circulation transient ischaemic attacks \(TIAs\)34%](#)[Posterior circulation strokes6%](#)[Acephalgic migraine46%](#)[Multiple sclerosis8%](#)[Occipital space occupying lesion5%](#)

The patient gives a strong history of positive visual symptoms such as flashing lights and dots, with no negative such as weakness, sensory loss or visual loss. This would be far more suggestive of a migrainous syndrome or primary retinal pathology than cerebrovascular insufficiency, where negative symptoms would be prominent. In addition, a diagnosis of TIA or

stroke should be suspicious in any patient with repeated stereotyped, similar symptoms over a long period of time. It is unlikely any patient will present with recurrent multiple TIAs without stroke over a 14 month period.

Acephalgic migraine is a frequently missed diagnosis of exclusion, where patients experience auras without a headache. Up to 38% of migraineurs experience migraine attacks without and with a headache, while 4% of migraineurs exclusively experience migraines without headaches<sup>1</sup>.

1. Russell MB, Olesen J. A nosographic analysis of the migraine aura in a general population. Brain. 1996;119 ( Pt 2):355.

## **Migraine: diagnostic criteria**

The International Headache Society has produced the following diagnostic criteria for migraine without aura:

<b>Point</b>	<b>Criteria</b>
<b>A</b>	At least 5 attacks fulfilling criteria B-D
<b>B</b>	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated) Headache has at least two of the following characteristics:
<b>C</b>	<ul style="list-style-type: none"><li>• 1. unilateral location*</li><li>• 2. pulsating quality (i.e., varying with the heartbeat)</li><li>• 3. moderate or severe pain intensity</li><li>• 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)</li></ul>

During headache at least one of the following:

<b>D</b>	<ul style="list-style-type: none"><li>• 1. nausea and/or vomiting*</li><li>• 2. photophobia and phonophobia</li></ul>
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<b>E</b>	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)
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\*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (seen in around 25% of migraine patients) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

If we compare these guidelines to the **NICE criteria** the following points are noted:

- NICE suggests migraines may be unilateral or bilateral
- NICE also give more detail about typical auras:

Auras may occur with or without headache and:

- are fully reversible
- develop over at least 5 minutes
- last 5-60 minutes

The following aura symptoms are atypical and may prompt further investigation/referral;

- motor weakness
- double vision
- visual symptoms affecting only one eye
- poor balance
- decreased level of consciousness.

#### Question 9 of 135

A 42-year-old male presents with double vision and weakness in his fingers, which he noticed when he repeatedly dropped his pen when trying to write at work. His symptoms appear to have onset over the past few days. He has no past medical history other than a recent episode of diarrhoea and vomiting about two weeks ago. He reports no limb weakness and no sensory loss. He denies any back pain or palpitations. On examination, there is a 3/5 weakness in finger flexion, finger extension and wrist extension in both hands, with no fatigability. No reflexes present in the lower or upper limbs. There is no ptosis or nystagmus but reduced eye movements in all directions. His finger-nose test demonstrates reduced coordination bilaterally and the patient has too little confidence to walk. Which investigation is most likely to be diagnostic?

[Anti-GM1 antibody20%](#)[Anti-GQ1b antibody55%](#)[MRI brain and whole spine8%](#)[Anti-MUSK \(muscle specific kinase\) antibody9%](#)[Anti-acetylcholine receptor antibody8%](#)

The patient has presented with a classic triad of ophthalmoplegia, ataxia and areflexia, which



should suggest Miller-Fisher syndrome, an acute onset demyelinating peripheral neuropathy recognised as a variant of Guillain-Barre Syndrome. Anti-GQ1b antibody is present in between 85-90% of patients with Miller-Fisher syndrome<sup>1</sup>.

Key differentials of MFS include myasthenia gravis, brainstem infarcts and brainstem encephalitis. In this case, the absence of fatigability and nystagmus rule against neuromuscular junction disorders and brainstem events respectively.

1. Chiba A, Kusunoki S, Obata H et al. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology*. 1993;43(10):1911.

## **Guillain-Barre syndrome**

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*)

### **Pathogenesis**

- cross reaction of antibodies with gangliosides in the peripheral nervous system
- correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated
- anti-GM1 antibodies in 25% of patients

### **Miller Fisher syndrome**

- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. The eye muscles are typically affected first
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- anti-GQ1b antibodies are present in 90% of cases

A 45-year-old Bangladeshi male presents with a 6-month history of bilateral reduced sensation on the tips of both his feet, which has gradually progressed on both legs to his low shins. His past medical history includes type 2 diabetes, diagnosed 7 years ago and reports good medication compliance with metformin 500mg BD alone, with a HbA1c of 48 mmol/mol (6.5%) two weeks ago. He is also currently in his ninth month of anti-tuberculosis treatment, having initially presented with a chronic cough, night sweats and weight loss. An induced sputum subsequently cultured positive for acid-fast bacilli. He did not bring in his medications but remembers being told they are 'the standard four then two drugs'. He takes no other medications and has no known drug allergies. On examination, tone, power and gait of his lower limbs are unremarkable. He demonstrates reduced sensation to light touch to his left lower shin and right mid-shin. Ankle jerks are absent bilaterally, plantars are downgoing bilaterally. What is the most likely diagnosis?

[Guillain-Barre syndrome \(GBS\)5%](#)[Chronic inflammatory demyelinating polyneuropathy \(CIDP\)8%](#)[Drug induced peripheral neuropathy77%](#)[Diabetic neuropathy5%](#)[Diabetic amyotrophy5%](#)

The patient describes a chronic sensory deficit in a peripheral nerve distribution. This is most likely isoniazid-induced peripheral neuropathy, classically interfering with vitamin B6 via an unknown mechanism. As a result, pyridoxine should be regularly prescribed in all patients taking isoniazid. GBS and CIDP classically present as combined motor and sensory syndromes, of duration less than and more than 4 weeks respectively. While diabetes-related peripheral neuropathy is possible, his glycosylated haemoglobin measurement, an accurate measure of the patient's serum glucose levels over the past 3 months, reflects very good control.

## **Drugs causing peripheral neuropathy**

Drugs causing a peripheral neuropathy

- amiodarone
- isoniazid
- vincristine
- nitrofurantoin
- metronidazole

Question 1 of 125

A 64-year-old woman attends neurology clinic after referral from her GP with intermittent episodes of facial pain. She had first noticed symptoms around 10 months previously and

recalled her first attack had occurred when taking her grand-children to a fireworks display. Pain episodes were described as a severe 'sawing' pain affecting the right side of her face that lasted one to two minutes before resolving completely. Since the onset the patient reported suffering from at least one attack on most days, with the frequency seeming to increase over time. On direct questioning she reported that on some occasions her nose had become blocked and she had felt sweaty during an episode but that these symptoms were not a major concern in comparison to the severe pain. The patient denied any other symptoms either at the time of the attack and was otherwise in good health with no recent history of weight loss. There was no family history of neurological disease.

A full neurological examination was performed with particular findings of normal pupillary reflexes, visual acuity and colour vision. There was no evidence of facial sensory deficit or facial nerve palsy. A peripheral neurological examination was likewise unremarkable.

Helpfully (although uncomfortably for the patient), a new episode of pain began during the course of the consultation. A further examination was conducted and conjunctival injection and slight eyelid oedema of the right eye were noted. In addition, the patient was noted to be sweating, markedly more profuse on the right side of her face. She also confirmed the onset of a blocked nose sensation at the onset of pain.

What is the most likely diagnosis causing the patients symptoms?

[Trigeminal neuralgia14%Multiple sclerosis5%Horners syndrome8%Short unilateral neuralgiform pain with autonomic symptoms62%Atypical trigeminal neuralgia10%](#)

The patients history certainly has features suggestive of trigeminal neuralgia, in particular the character and episodic nature of the pain and that the first episode was particularly memorable. However, the presence of autonomic features associated with attacks points strongly towards the variant short unilateral neuralgiform pain with autonomic symptoms (SUNA) as the correct diagnosis. The distinction is clinically relevant as individuals with autonomic symptoms achieved less benefit from microvascular decompression compared to individuals with trigeminal neuralgia.

Atypical trigeminal neuralgia is the diagnosis made when an individual suffers from persistent lower intensity pain between exacerbations, in contrast to the complete resolution of pain seen in trigeminal neuralgia. Horners syndrome would not cause episodic autonomic symptoms and is not normally associated with pain. Multiple sclerosis is an important differential for trigeminal neuralgia but the patients normal baseline neurological examination and prominent autonomic symptoms make this less likely. If uncertainty persists after clinical assessment, MRI scanning to assess for demyelination plaques is the appropriate investigation.

Zakrzewska J, Linskey M. Trigeminal neuralgia. BMJ 2014;348:g474.

## Trigeminal autonomic cephalalgias

### Trigeminal autonomic cephalalgias (TACs)

- cluster headache
- paroxysmal hemicrania
- hemicrania continua
- short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome)
- short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)

### Question 5 of 125

A 73 year old gentleman is admitted to the medical assessment unit with a fall. A collateral history from his wife reveals that he has been having frequent falls (nearly 2-3 times a week) for the last 4 months. This has resulted in multiple admissions where a chest infection is thought to be the main cause for his deterioration. His wife also states he is having problems swallowing, chokes on his food frequently and has not been himself recently with frequent bouts of aggression. On examination you note the patient has an expressionless face, and kyphosed posture and mild tremor bilaterally. He has cogwheeling of both upper limbs. Examination of his legs is unremarkable. On inspection of his gait, it appears parkinsonian in character, but you stop him only after a few steps as he seems unsteady. On cranial nerve examination you note he has difficulty following your finger downwards but the remainder of the cranial nerve examination is normal. Given these features, what is the most likely underlying diagnosis?

[Multiple system atrophy16%Idiopathic Parkinsons disease6%Progressive supranuclear palsy65%Vascular Parkinsonism5%Lewy body dementia8%](#)

There is no doubt that this patient has an element of Parkinsons disease, the clues to the underlying condition include:

- The SYMMETRICAL tremor compared with the ASYMMETRICAL tremor of idiopathic Parkinsons.
- Swallowing difficulties suggesting repeated admissions for aspiration pneumonia.
- Changes in personality.
- Truncal instability and rigidity > limbs.
- Inability of look downwards (Vertical gaze palsy).

Parkinsons Plus syndromes:

- Progressive supranuclear palsy (PSP, also known as Steele-Richardson-Olszewski syndrome) - Characterised by early postural instability, frequent falls, truncal rigidity, asymmetrical onset, speech and swallowing problems, vertical gaze palsy.
- Multiple system atrophy - (MSA, also known as Shy-Drager syndrome). Autonomic features specifically postural blood pressure drop, bladder/bowel dysfunction, cerebellar and/or pyramidal signs.
- Lewy body dementia - Visual hallucinations accompanying dementia.
- Vascular parkinsons - Parkinsonism worse in the legs than the arms.
- Cortico-basal degeneration (CBD) - Asteroagnosia (inability to recognise objects by touch), akinetic rigidity involving one limb. Some patients may experience the 'alien limb phenomenon'.

NB: Knowledge of this differential is also vital for PACES examinations.

## **Progressive supranuclear palsy**

### Overview

- aka Steele-Richardson-Olszewski syndrome
- a 'Parkinson Plus' syndrome

### Features

- impairment of vertical gaze (down gaze worse than up gaze - patients may complain of difficulty reading or descending stairs)
- parkinsonism
- falls
- slurring of speech
- cognitive impairment

### Management

- poor response to L-dopa

### Question 6 of 125

A 60 yr old woman went swimming with her family, and after finishing her swim and having a shower, her daughter noted that she became confused suddenly, repetitively asking if they had gone for a swim today. She could not remember events that occurred in the past 24 hours, and when told the answers to her questions, would ask the same question 5 minutes later. There was no change in her personality, no change in her speech, nor any muscle weakness. She is able to recall her address, the names of her daughters and husband, and her date of birth.

Her daughter said her mother did not suffer any trauma during the swim, and did not lose consciousness anytime throughout the day. The patient's past medical history includes hypertension and depression, and she takes ramipril 2.5mg once daily, and citalopram 20mg once daily.

On examination the patient was alert, but constantly asked where she was and why was she in hospital. She was afebrile, heart rate 80 bpm, blood pressure 138/68 mmHg, respiratory rate of 18 breaths per minute, and oxygen saturation of 99% on air. Neurological examination was unremarkable, but her abbreviated mental test score was 6/10.

Her investigation results were as follow:

C Reactive protein	4 mg/l
Haemoglobin	14.8 g/dl
White cell count	$5.6 \times 10^9/L$
Na+	142 mmol/l
K+	4.3 mmol/l
Urea	4.2 mmol/l
Creatinine	68 $\mu$ mol/l
Corrected calcium	2.32 mmol/l
Plasma glucose	5.8 mmol/l

Computer Tomography (CT) head scan No acute intracranial pathology.

Over the next 12 hours, her memory improves and she is discharged from the observation ward.

What is the best advice for the patient with regards to driving in the future?

She can drive 4 weeks after the event if the cause has been identified and treated18%DVLA need not be notified, no driving restrictions49%She must be symptom free for 1 year before being eligible to drive9%DVLA must be informed, and her licence will be revoked for 6 months10%She must cease driving until there is satisfactory control of her symptoms13%

This lady has suffered an episode of transient global amnesia, a neurological condition characterised by acute short term memory loss, lasting no more than 24 hours. Patients often developed perseveration, with repetitive questioning as they are unable to keep short term

memory, but are able to recall long term memories. The aetiology of this condition is unknown.

DVLA guidelines for transient global amnesia are that as long as epilepsy, any sequelae from head injury and other causes of altered awareness have been excluded, there are no restrictions on driving and the DVLA need not be informed.

## **DVLA: neurological disorders**

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Epilepsy/seizures - all patient must not drive and must inform the DVLA

- first unprovoked/isolated seizure: 6 months off if there are no relevant structural abnormalities on brain imaging and no definite epileptiform activity on EEG. If these conditions are not met then this is increased to 12 months
- for patients with established epilepsy or those with multiple unprovoked seizures:
- → may qualify for a driving licence if they have been free from any seizure for 12 months
- → if there have been no seizures for 5 years (with medication if necessary) a 'til 70 licence is usually restored
- withdrawal of epilepsy medication: should not drive whilst anti-epilepsy medication is being withdrawn and for 6 months after the last dose

## **Syncope**

- simple faint: no restriction
- single episode, explained and treated: 4 weeks off
- single episode, unexplained: 6 months off
- two or more episodes: 12 months off

## **Other conditions**

- stroke or TIA: 1 month off driving, may not need to inform DVLA if no residual neurological deficit
- multiple TIAs over short period of times: 3 months off driving and inform DVLA
- craniotomy e.g. For meningioma: 1 year off driving\*
- pituitary tumour: craniotomy: 6 months; trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'

- narcolepsy/cataplexy: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'
- chronic neurological disorders e.g. multiple sclerosis, motor neuron disease: DVLA should be informed, complete PK1 form (application for driving licence holders state of health)

\*if the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free

#### Question 7 of 125

A 52-year-old male is brought to the emergency department by his concerned wife after tripping and falling down a flight of 12 stairs at home, hitting his head on the way down. The patient himself is not concerned and believes he could have stayed at home.

He denies having a headache, reports no nausea or vomiting, no seizures and did not lose consciousness between the fall and when you examine him. He is not taking any regular medications including anticoagulants and remembers the whole episode except for about 20 seconds after landing at the bottom of the floor. On examination, he has no limb weakness or loss of sensation. His pupils are equal and reactive bilaterally. What is the most appropriate management?

[Discharge, no further investigations required18%](#)[Discharge, outpatient CT head within 72 hours8%](#)[Observe for 24 hours and discharge if no deterioration17%](#)[CT head immediately16%](#)[CT head within 8 hours of injury41%](#)

The patient has presented following a mechanical fall with a dangerous mechanism of injury.

#### **Head injury: NICE guidance on investigation**

NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging. The latter group are also divided into two further cohorts, those who require an immediate CT head and those requiring CT head within 8 hours of injury:

CT head immediately

- GCS < 13 on initial assessment



- GCS < 15 at 2 hours post-injury
- suspected open or depressed skull fracture.
- any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- post-traumatic seizure.
- focal neurological deficit.
- more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- age 65 years or older
- any history of bleeding or clotting disorders
- dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs)
- more than 30 minutes' retrograde amnesia of events immediately before the head injury

If a patient is on warfarin who have sustained a head injury with no other indications for a CT head scan, perform a CT head scan within 8 hours of the injury.

#### Question 8 of 125

A 23-year-old university student presented with a year long history of occipital headache. This was worse on coughing, sneezing and straining and partially relieved by lying flat. On one occasion the headache had been associated with vomiting. She had previously consulted her family doctor who was treating her for migraine. Over the past two months she had noticed pain in her both arms and felt unsteady on her feet.

On examination touching her arms caused pain and there was reduced appreciation of pinprick and temperature sensation throughout both arms. Tone, power and reflexes in the upper limbs were normal. On testing upper limb co-ordination there was some past-pointing and a very mild intention tremor. On inspection of the feet there was pes cavus and Rombergs test was positive. Again tone, power and reflexes were normal in the lower limbs and plantars were downgoing. Proprioception was impaired with absent joint position sense until the level of the knee. Vibration sensation was impaired in both feet.

Given the clinical findings outlined above which of the following is the most likely diagnosis?

[Syringomyelia36%](#) [Friedrichs ataxia23%](#) [Brown-Sequard syndrome7%](#) [Charcot-Marie-Tooth disease30%](#) [Multiple sclerosis5%](#)

Syringomyelia results from the formation of a fluid filled cavitation (called a syrinx) within the central canal of the spinal cord. The most common cause of a syrinx is obstruction to the flow of cerebrospinal fluid (CSF) by an Arnold Chiari malformation. An Arnold Chiari malformation is a developmental abnormality in which the cerebellar tonsils project through the foramen magnum and sit in a position which is normally occupied by the cervical spinal cord.

In this case the patient has features suggestive of an underlying Arnold Chiari malformation: occipital headache exacerbated by valsalva manoeuvre (coughing, sneezing and straining), pes cavus and cerebellar signs (past pointing and intention tremor in the upper limbs).

She also has features of an associated syringomyelia. The spinothalamic tracts are involved early in the process due to their decussation within the cord. This means that there is loss of pain and temperature sensation corresponding to the level of the syrinx. This often occurs in a shawl-like distribution. Hyperalgesia and allodynia are also seen in the upper limbs in some cases.

As the syrinx enlarges the dorsal columns are affected resulting in loss of proprioception and vibration sensation in the lower limbs. This explains the positive Rombergs test which indicates that there is a proprioceptive problem.

If the syrinx expands further the anterior horn cells can be affected resulting in wasting and weakness in the hands.

Friedrichs ataxia is an autosomal recessive inherited condition in which there is progressive ataxia, dysarthria, loss of proprioceptive and vibration sensation and weakness.

Brown-Sequard syndrome results from a lateral hemisection of the spinal cord. It presents with a loss of pain and temperature sensation on the side of the body contralateral to the lesion and a hemiplegia and loss of vibration sensation and proprioception on the ipsilateral side to the lesion.

Charcot-Marie-Tooth (also known as Hereditary Sensory and Motor neuropathy) encompasses a group of inherited conditions which present in mid-adult life with peripheral neuropathy. Patients commonly have pes cavus and often present with foot drop.

Multiple sclerosis (MS) can present in a variety of ways with cerebellar features, optic neuritis, paraesthesiae and transverse myelitis all being reported. Although in theory many of the clinical features in this question could be explained by an underlying diagnosis of MS, the clinical presentation here is typical of syringomyelia secondary to an underlying Arnold Chiari malformation.

## **Syringomyelia**

## Overview

- development of cavity (syrinx) within the spinal cord
- if extends into medulla then termed syringobulbia
- strongly associated with the Arnold-Chiari malformation

## Features

- maybe asymmetrical initially
- slowly progressives, possibly over years
- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
- loss of reflexes, bilateral upgoing plantars
- also seen: Horner's syndrome

## Question 1 of 115

A 42-year-old woman attends neurology clinic for review of her treatment strategy for multiple sclerosis. The patient had first developed symptoms of multiple sclerosis five years previously. Her first episode had involved sensory loss and motor weakness affecting her left leg. An MRI brain scan conducted at this time had demonstrated multiple lesions suggestive of multiple sclerosis. At this point in time, the patient had decided against receiving disease modifying therapy.

One year after her first episode, the patient suffered an episode of optic neuritis. A repeat MRI scan had demonstrated a progression of the previously observed radiographic lesions. Subsequently, the patient had been initiated on treatment with interferon beta. This treatment was continued for two years during which time the patient suffered no further relapses of multiple sclerosis. However, the patient found the unwanted effects of interferon beta to be progressively harder to tolerate and she eventually decided against continuing with this treatment. A subsequent trial of glatiramer acetate was quickly halted due to the patient experiencing severe symptoms of flushing.

Following the cessation of disease-modifying therapy, the patient had experienced multiple further relapses, including one episode where she had required hospitalisation due to cranial nerve involvement. Further assessment during this period found that the patient met the local criteria for aggressive or highly active multiple sclerosis. Accordingly, later line therapies were discussed with the patient who was keen to proceed.

Aside from her history of multiple sclerosis the patient suffered from no other significant

medical problems and took no regular medications. The patient was a science teacher that had been unable to work for the past year due to her multiple relapses.

The later line therapy recommended for the patient is natalizumab. What is the essential investigation that must be completed prior to initiation of treatment with natalizumab?

[Transthoracic echocardiogram 10% JCV antibody status 64% Pulmonary function tests 9% Thyroid function tests 5% CMV antibody status 12%](#)

The patient has highly active multiple sclerosis causing significant morbidity. While she had obtained benefit from the standard initial therapies interferon beta and glatiramer acetate, these treatments were ultimately not tolerated. In this situation, consideration of escalation to second-line disease-modifying therapy is appropriate. Observational studies have reported that escalation from a first-line therapy to a second-line drug reduces relapse rate at one year.

Evidence suggests that alemtuzumab, natalizumab and fingolimod outperformed other disease-modifying therapies at preventing relapse at 2 years. In addition, natalizumab also reduced 2-year disability progression rates.

Natalizumab is strongly associated with progressive multifocal leukoencephalopathy, an infection of the central nervous system with the John Cunningham virus (JCV). Therefore, JCV antibody status is an essential part of assessing an individual for treatment with natalizumab. Patient's who are seropositive for JCV are not treated with natalizumab or switched to another drug.

Wingerchuk D, Weinshenker B. Disease-modifying therapies for relapsing multiple sclerosis. *BMJ* 2016;354:i3518.

## **Multiple sclerosis: management**

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

### **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

### **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

## **Some specific problems**

### Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

### Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

### Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying
  - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

### Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line
- Question 2 of 115
- A 74-year-old female has been admitted to the stroke unit following a significant right middle cerebral artery infarct. A dense left side sensori-motor syndrome and significantly impaired swallowing mechanisms were noted. Nursing staff insert a nasogastric (NG) tube after the patient failed her swallow screen and NG feed is immediately started. Around 72 hours after the feed was commenced, her blood sugar was noted to be 16 mmol/l, with no serum or urinary ketones. Her only past medical history was paroxysmal atrial fibrillation and no known diagnosis of diabetes mellitus. She took aspirin 75mg only prior to admission. What is the optimal management of her hyperglycaemia?
- [Prescribe 6 units actrapid as required when BM > 10 mmol/l17%Stop the NG feed8%Prescribe biphasic insulin twice daily36%Prescribe warfarin as per loading regime6%Repeat the BM in 4 hours time, no action at present33%](#)
- The most likely cause of this patient's raised blood sugar is NG feed associated hyperglycaemia. Patients with hyperglycaemia should never be prescribed PRN actrapid nor should the NG feed be stopped, as the patient demonstrates no signs of aspiration and has no other means of obtaining nutrition. The Joint British Diabetes Society 2012 guidelines recommend a target BM of between 6 and 12 mmol/l for hyperglycaemic patients on NG feed with insulin to be started when BM over 12 mmol/l. The insulin regime of choice is a biphasic insulin such as humulin M3, with a mixture of intermediate and short acting insulin, prescribed twice daily, at the start and middle of the NG feed<sup>1</sup>.

1. Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes. Joint British Diabetes Societies (JBDS) for inpatient care. June 2012

#### Question 6 of 115

A 14-year-old boy presents his third generalised seizure over the past 72 hours, despite recently being started on sodium valproate by a neurologist for recurrent seizures 6 weeks ago, with worsening vision at night and hearing loss bilaterally. The patient has a number of myoclonic jerks as you arrive. On examination, his heart sounds are unremarkable but you notice a tachycardia at 140 and regular. The ECG is shown below:



© Image used on license from [Dr Smith, University of Minnesota](#)



The patient is uncooperative to further neurological examination but you notice sluggishly reactive pupils of equal size. His mother reports that he has been educated in a special needs school for the past 5 years but had been attending the local primary school until aged 9, when he dropped further behind than his peers. Which investigation produces the underlying diagnosis?

[MRI](#)16% [Lumbar puncture](#)6% [Electroencephalogram \(EEG\)](#)10% [Cardiac electrophysiology studies](#)13% [Muscle biopsy](#)55%

The patient is a young male presenting with cognitive impairment developing after a period of normal development, seizures, myoclonic jerks, Wolff-Parkinson-White syndrome and worsening vision (consistent with optic atrophy). The unifying diagnosis is that of myoclonic epilepsy with ragged red fibres (MERRF), which is a mitochondrial DNA disorder diagnosed by ragged red fibres on muscle biopsy.

## Mitochondrial diseases

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- all children of affected males will not inherit the disease
- all children of affected females will inherit it
- generally encode rare neurological diseases
- poor genotype:phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy)

## Histology

- muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples include:

- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

## Question 8 of 115

A 50-year-old man is seen in the Emergency Department with fevers. He has been feeling generally unwell for the last 3 days and has just returned from a 2 week stay with his sister who lives on the other side of the U.K. He has had a mild non-productive cough and shortness of breath. He has had no vomiting, diarrhoea, dysuria or abdominal pain.

He has a past medical history of epilepsy, schizophrenia, hypertension and diet-controlled type 2 diabetes.

On examination he has a temperature of 38.3 °C and is saturating at 94% on room air. His heart rate is 111 beats per minute and blood pressure is 118/75 mmHg. He looks clammy and pale but systems examination is otherwise unremarkable.

His chest x-ray shows clear lung fields.

His blood tests are as follows:

Hb	140 g/l	Na <sup>+</sup>	141 mmol/l
Platelets	443 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.7 mmol/l
WBC	1.5 * 10 <sup>9</sup> /l	Urea	7 mmol/l
Neuts	0.6 * 10 <sup>9</sup> /l	Creatinine	98 µmol/l
Lymphs	0.5 * 10 <sup>9</sup> /l	CRP	170 mg/l

He is started on broad spectrum antibiotics and fluids.



Which drug is most likely to have precipitated this condition?

[Clobazam5%Clozapine72%Phenytoin9%Sodium valproate6%Venlafaxine8%](#)

This gentleman has neutropenic sepsis. The antipsychotic clozapine is well documented to cause agranulocytosis, neutropenia and lymphopenia. Patients on clozapine must be registered with the monitoring service specific to their brand of the drug and have regular drug levels and full blood counts. This gentleman has been travelling and has likely missed his monitoring appointment.

Clobazam side effects include drowsiness and confusion.

Phenytoin can cause leucopenia but this is unlikely in the absence of its other extensive side effect profile which includes drowsiness, tremor, gum hypertrophy, acne and hirsutism.

Sodium valproate also has a broad side effect profile which includes nausea, diarrhoea, weight gain, extra-pyramidal symptoms and hair loss. Again leucopenia is a documented side effect but rare.

Venlafaxine is associated with changes to serum cholesterol, hypertension, micturition disturbance and vasodilatation.

Reference: British National Formulary.

## **Atypical antipsychotics**

Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines. The main advantage of the atypical agents is a significant reduction in extra-pyramidal side-effects.

Adverse effects of atypical antipsychotics

- weight gain
- clozapine is associated with agranulocytosis (see below)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

## Examples of atypical antipsychotics

- clozapine
- olanzapine
- risperidone
- quetiapine
- amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication

## Adverse effects of clozapine

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients
- Question 9 of 115
- A 48-year-old male presents with a sudden onset occipital headache onset 2 and half hours ago, associated with slurred speech, vomiting and unsteadiness in all movements. In the 90 minutes after admission to the emergency department, it was noted that the patient became increasingly drowsy, deteriorating from a GCS of 15 on admission to E3 V4 M5. On examination, pupils are equal, his speech is dysarthric and bilateral plantars are downgoing. You are unable to elicit more formal power, tone or sensation examination in the patient. An initial CT head is unremarkable but a subsequent MRI head with diffusion weighting sequences demonstrates restricted diffusion in bilateral cerebellar hemispheres with significant swelling around the cerebellum, brainstem and aqueduct. GCS currently 14/15 at 10 hours post-event. You have initiated aspirin 300mg and inserted a nasogastric tube. What is the appropriate management?
- [Add clopidogrel 300mg5%Start warfarinisation5%Thrombolysis8%Discuss with neurosurgery for decompressive posterior craniectomy69%Hourly neuro observations with empirical anti-seizure medications12%](#)
- This patient is critically unwell. He has presented with a posterior circulation infarct significant oedema around a very tight part of the neuro-anatomy. Although pupils are currently equal and reactive, the drop in GCS is a major concern. It may not be possible to illicit upper motor neurone signs in the hyperacute phase after a stroke. The most concerning complication at this stage is a progression towards obstructive hydrocephalus from CSF flow blockage at the aqueduct or 3rd or 4th ventricle. Prophylactic posterior craniectomy must be considered in such a young patient, discussion with neurosurgery is essential.

### Question 10 of 115

A 76-year-old residential home resident was seen in the neurology clinic. She had a history of Alzheimer's disease, and her behaviour had become progressively more challenging over the past 4 months, for which she had been started on regular haloperidol.

The residential home staff had reported that over the previous four weeks she had developed involuntary movements of her mouth, with frequent tongue protrusion and lip-smacking. There were no neurological deficits and no history of blackouts. Two weeks ago she was reviewed by the general practitioner who stopped her haloperidol. However, her involuntary facial movements became more prominent following this.

On examination, she appeared well, other than continuous involuntary lip-smacking, tongue protrusion, and frequent eye-blinking. She was alert, and there were no focal neurological deficits.

What is the most likely cause for her symptoms?

[Temporal lobe epilepsy12%](#)[Progression of Alzheimer's disease5%](#)[Chronic tardive dyskinesia68%](#)[Frontotemporal dementia10%](#)[Huntington's disease6%](#)

First-generation antipsychotic agents (e.g. haloperidol, chlorpromazine) may result in extrapyramidal side effects due to relatively non-selective dopamine blockade. This may manifest as chronic tardive dyskinesia, as in this case. Clinical features of chronic tardive dyskinesia include involuntary repetitive movements, such as lip-smacking, tongue protrusion, and distal chorea. It is treated by withdrawal of the offending agent, though it may paradoxically worsen in the first few weeks of stopping the drug. The typical features and temporal relationship make chronic tardive dyskinesia secondary to haloperidol the most likely diagnosis in this case. Other extrapyramidal side effects include acute dystonic reactions, akathisia, and Parkinsonism.

Lip-smacking may occur in complex partial seizures in temporal lobe epilepsy, but this would be associated with impaired consciousness and would only last a few minutes. Advanced Alzheimer's disease may be associated with involuntary movements (e.g. myoclonus), but is not typically associated with dyskinesias. Parkinsonism may occur in frontotemporal dementia, but dyskinesia is not associated. A new diagnosis of Huntington's disease would be very unlikely in this age group.

### Antipsychotics

Antipsychotics act as dopamine D2 receptor antagonists, blocking dopaminergic transmission in the mesolimbic pathways. Conventional antipsychotics are associated with problematic

extrapyramidal side-effects which has led to the development of atypical antipsychotics such as clozapine

#### Extrapyramidal side-effects

- Parkinsonism
- acute dystonia (e.g. torticollis, oculogyric crisis)
- akathisia (severe restlessness)
- tardive dyskinesia (late onset of choreoathetoid movements, abnormal, involuntary, may occur in 40% of patients, may be irreversible, most common is chewing and pouting of jaw)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke
- increased risk of venous thromboembolism

#### Other side-effects

- antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- sedation, weight gain
- raised prolactin: galactorrhoea, impaired glucose tolerance
- neuroleptic malignant syndrome: pyrexia, muscle stiffness
- reduced seizure threshold (greater with atypicals)
- prolonged QT interval (particularly haloperidol)

#### Question 1 of 105

A 42 year old caucasian man presents to his GP because of concerns about weight gain. He has put on 10kg in weight in the past 6 months but has been eating and exercising the same amounts for the past few years. The GP decides to do some further investigations and finds the following abnormalities. He tells you that he was on a medication for schizophrenia but this was changed one year ago due to abnormal movements. In the past year he has also been given medications to help with symptoms of nausea and has recently started medication for gynaecomastia.

Hb 13.8 g/dl  
Platelets  $154 \times 10^9/l$   
WBC  $3.8 \times 10^9/l$   
Neuts  $1.5 \times 10^9/l$

Lymphs  $1.0 \times 10^9/l$

Eosinos  $1.2 \times 10^9/l$

Fasting glucose 11.9 mmol/l

Prolactin 264 mu/l

ECG: sinus rhythm 84/min QTC 462ms

Which drug is most likely to have caused these abnormalities?

[Haloperidol13%Clozapine54%Bromocriptine13%Domperidone13%Ondansetron7%](#)

Clozapine is an atypical antipsychotic that is used in treatment resistant schizophrenia and also if there has been tardive dyskinesia on a previous antipsychotic which is described in this question. Clozapine can cause neutropaenia, eosinophilia and prolongation of the QTc as well as increased weight gain and reduced insulin tolerance which are all seen in this individual

Haloperidol can also cause QTc prolongation. It is less likely to cause weight gain and reduced glucose tolerance than clozapine and it is not associated with neutropaenia or eosinophilia. Haloperidol more commonly causes tardive dyskinesia than Clozapine and it is possible that he was on this before switching due to hyperprolactinaemia and tardive dyskinesia

Bromocriptine is a treatment designed to reduce prolactin levels and does not cause reduced glucose tolerance or neutropaenia.

Domperidone can cause prolonged QTc but would not explain any of the other abnormalities.

Ondansetron can cause prolongation of the QTc but does not cause any of the other abnormalities described here

### **Atypical antipsychotics**

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Adverse effects of atypical antipsychotics

- weight gain
- clozapine is associated with agranulocytosis (see below)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

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Examples of atypical antipsychotics

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Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication

Adverse effects of clozapine

- agranulocytosis (1%), neutropenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients

Question 2 of 105

A 28-year-old lady presents to the emergency department with a 4-day history of generalised headache that is worse on lying down. She reports it has gradually become worse and she has also noticed blurred vision since yesterday. Her past medical history includes chronic back pain, acne and anxiety. On examination, she is noted to be overweight. Fundoscopy shows papilloedema. Further investigations point to a diagnosis of idiopathic intracranial hypertension. Which of the following of her medications is associated with this condition?

[Tramadol10%](#) [Tetracycline antibiotics57%](#) [Diazepam6%](#) [Amitriptyline14%](#) [Ibuprofen13%](#)

Associated medications include, but are not limited to:

- tetracycline antibiotics
- isotretinoin
- contraceptives

- steroids
- levothyroxine
- lithium
- cimetidine

## **Idiopathic intracranial hypertension**

Idiopathic intracranial hypertension (also known as pseudotumour cerebri and formerly benign intracranial hypertension) is a condition classically seen in young, overweight females.

### Features

- headache
- blurred vision
- papilloedema (usually present)
- enlarged blind spot
- sixth nerve palsy may be present

### Risk factors

- obesity
- female sex
- pregnancy
- drugs\*: oral contraceptive pill, steroids, tetracycline, vitamin A, lithium

### Management

- weight loss
- diuretics e.g. acetazolamide
- topiramate is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

\*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

### Question 3 of 105

A 35 year old mechanic attends the emergency department following an injury at work. He has suffered a serious laceration to the upper arm. While suturing, the doctor notices multiple cuts and burns on both arms.

On examination there is marked wasting of brachioradialis and the small muscles in both hands, with mild hyporeflexia of the biceps and brachioradialis tendons. He is weak in both arms, distally more so. His lower limb and cranial nerve examination is unremarkable. On testing upper limb sensation, vibration and proprioception are intact but there appears to be reduced pain and temperature sensation over the C3/C4/C5 dermatomes. What is the most useful investigation?

[Lumbar puncture6%](#) [Nerve conduction studies18%](#) [MRI Brain6%](#) [Electromyography9%](#) [MRI cervico-thoracic spine62%](#)

The presence of loss of pain and temperature sensation in a 'cape like' distribution is highly suggestive of syringomyelia. A fluid filled cavity within the cord develops, typically between C2 to T9, compressing the cord from inside to out. Consequently the spinothalamic tracts are the first to be affected in a symmetrical distribution.

There are a number of aetiologies, but it should be noted that there is an association with Arnold Chiari malformation Type 1. It is sensible to investigate for a compressive cord lesion in the first instance; imaging of the brain may be considered if syringomyelia is detected. An MRI cervico-thoracic cord would be the most sensitive method of detecting syringomyelia.

National Institute of neurological disease and stroke: syringomyelia fact sheet  
<http://www.ninds.nih.gov/disorders/syringomyelia/detailsyringomyelia.htm>

## Syringomyelia

### Overview

- development of cavity (syrinx) within the spinal cord
- if extends into medulla then termed syringobulbia



- strongly associated with the Arnold-Chiari malformation

## Features

- maybe asymmetrical initially
- slowly progressive, possibly over years
- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
- loss of reflexes, bilateral upgoing plantars
- also seen: Horner's syndrome

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## Question 5 of 105

A 36-year-old female presents to clinic with transient visual loss. She reports three episodes over the last few months where her 'turns black' in both eyes despite being alert. This lasts for a few seconds and is then followed by a unilateral throbbing headache associated with nausea and phonophobia. It is worse on exertion and lasts for a couple of days. On examination her visual acuity is 20/20 bilaterally, her visual fields are normal and fundoscopy is unremarkable.

What is the most likely diagnosis?

[Transient ischaemic attack](#)4% [Amaurosis fugax](#)16% [Anterior ischaemic optic neuropathy](#)7% [Temporal arteritis](#)5% [Migraine with aura](#)68%

The headache in this patient is very typical of migraine which can be preceded by an aura lasting between 5 minutes to an hour usually. This patient's visual loss was relatively brief and in the context of unilateral vision loss would certainly raise the possibility of transient ischaemic attack (TIA). However, she reports her vision turned black in both eyes which would be very unlikely with a TIA as there would have needed to be simultaneous involvement of both anterior visual pathways. Since there is isolated bilateral transient visual loss if this was a TIA it would be of the occipital cortex from occlusion of the posterior cerebral artery although this is very unlikely given it does not appear to be a homonymous hemianopia she describes, and there is a characteristic history of migraine which is the most common cause of transient bilateral visual loss in young adults. Amaurosis fugax specifies a type of TIA, which typically causes unilateral visual disturbance.

Temporal arteritis represents an arteritic form of anterior ischaemic optic neuropathy. Temporal arteritis tends to present later in life and may be associated with other symptoms like scalp tenderness, and jaw claudication. The non-arteritic form of anterior ischaemic optic neuropathy tends to be related to cardiovascular factors, and therefore again presents later in life and more commonly restricted to one eye.

## Migraine: diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for migraine without aura:

Point	Criteria
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated) Headache has at least two of the following characteristics:
C	<ul style="list-style-type: none"><li>1. unilateral location*</li><li>2. pulsating quality (i.e., varying with the heartbeat)</li><li>3. moderate or severe pain intensity</li><li>4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)</li></ul>

During headache at least one of the following:

D	<ul style="list-style-type: none"><li>1. nausea and/or vomiting*</li><li>2. photophobia and phonophobia</li></ul>
E	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

\*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (seen in around 25% of migraine patients) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

If we compare these guidelines to the **NICE criteria** the following points are noted:

- NICE suggests migraines may be unilateral or bilateral
- NICE also give more detail about typical auras:

Auras may occur with or without headache and:

- are fully reversible
- develop over at least 5 minutes
- last 5-60 minutes

The following aura symptoms are atypical and may prompt further investigation/referral;

- motor weakness
- double vision
- visual symptoms affecting only one eye
- poor balance
- decreased level of consciousness.

#### Question 1 of 99

A 22 year old woman is brought to the Emergency Department by ambulance. She is accompanied by her boyfriend who tells you he thinks she has taken a deliberate overdose of up to 80 fluoxetine tablets (20mg) within the past eight hours. On assessment her airway is patent but threatened with a respiratory rate of 26 and peripheral oxygen saturations of 97% on air. Her chest is clear. The heart rate is 118bpm and the blood pressure is 98/39mmHg. Capillary blood glucose is 5.0mmol/L. The ECG shows a sinus tachycardia with QRS duration 114msec and corrected QT interval 575msec. She is globally hypertonic, shivering, nauseated, vomiting and sweaty with a tympanic temperature of 37.7°C and dilated pupils and prominent clonus. She suddenly has a prolonged tonic-clonic seizure and receives 20mg intravenous diazepam with no response after 15 minutes.

Which of the following is the safest subsequent intervention in this patients management?

[Further 10mg intravenous diazepam](#)7% [10mg rectal diazepam](#)5% [Phenytoin infusion](#)20mg/kg22% [Levetiracetam 1000mg intravenous infusion](#)8% [Intubate and ventilate](#)59%

Care should be taken in status epilepticus due to drug toxicities refractory to benzodiazepines; phenytoin is cardiotoxic and phenobarbital is a potent respiratory depressant. Intubation is often safest

Seizures in drug overdoses are relatively common occurrences and may be related to the drug itself, its metabolites or as a consequence of electrolyte derangements. Generally, brief and isolated convulsions do not require specific treatment and may be managed conservatively. Recurrent or prolonged seizures predispose to injury, hypoxia and renal failure; first line treatment is with benzodiazepines such as diazepam, lorazepam or midazolam. In pre-hospital environments, or in those patients in whom intravascular access is yet to be established, rectal diazepam is a reasonable route of administration since it is rapidly absorbed across the bowel wall and enters the pudendal vasculature and is rapidly distributed to the central nervous system without passing through the liver first. If intravenous access is present however, as in the above

patient, this route should be used. If a choice of intravenous benzodiazepines is available, lorazepam should be used preferentially since diazepam emulsion has a high risk of thrombophlebitis. In the above vignette, 20mg intravenous diazepam has been administered with no clinical effect; this is the maximal dose permitted in 4 hours and further doses are unlikely to be helpful. Second line agents which are recommended in persistent seizure activity are phenytoin or phenobarbital. Care must be taken when using phenytoin as an anti-seizure drug in overdoses since it exerts its anti-epileptic effects by inhibiting sodium channels; this is an effect shared by many cardiotoxic drugs taken in overdose. Co-administration of phenytoin and many drugs may lead to significant widening of the QRS duration, prolongation of the QT interval and ultimately to torsades de pointes, ventricular tachycardias and cardiac arrest. Phenytoin should not be used when there is any ECG evidence of prolongation of QRS or QT phases.

Levetiracetam is a relatively new antiepileptic drug which works by modulating NMDA glutamate neurotransmission. It can be given intravenously when oral routes are unavailable but it is licensed only for use in established epilepsy and not as a treatment for status epilepticus or drug induced seizures and should not be used here.

Phenobarbital is a drug which is rarely used in status epilepticus due to the risk of significant respiratory depression. It is however considered a second line agent to treat seizures as an alternative to phenytoin and could potentially be used here, although given the rest of the clinical information and probable evolving serotonin syndrome, intubation, ventilation and paralysis is probably safest.

In poisonings with cardiotoxic drugs, use of antiarrhythmic drugs to control ECG anomalies is not recommended; intravenous sodium bicarbonate may be given in patients with prolongation of QRS duration and magnesium sulphate can be given in QT prolongation or torsades de pointes, although the QT duration may not reduce but the incidence of escape rhythms is lessened.

## **Status epilepticus**

This is a medical emergency. The priority is termination of seizure activity, which if prolonged will lead to irreversible brain damage. First-line drugs are benzodiazepines such as diazepam or lorazepam. If ineffective within 10 minutes it is appropriate to start a second-line agent such as phenytoin, sodium valproate, levetiracetam, or phenobarbital. If no response within 30 minutes from onset, then the best way to achieve rapid control of seizure activity is induction of general anaesthesia.

A 50-year-old woman is admitted to the Emergency Department. She has a long history of drug and alcohol abuse and is well known to staff. From her records you can see that she is known to have chronic hepatitis C. A HIV test 6 months ago was negative. She is brought in after having a seizure whilst in police custody. The paramedics describe a generalised tonic-clonic seizure which terminated after 10mg of rectal diazepam was administered.

On admission she is drowsy and demands morphine for her headache. Her pulse is 84/min, blood pressure 116/80 mmHg and temperature 37.2°C. A full neurological examination is not possible as she is drowsy and combative.

A CT scan is arranged:



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What is the most likely diagnosis?

[Glioblastoma multiforme](#)47%[Cerebral toxoplasmosis](#)33%[Meningioma](#)8%[Extradural haematoma](#)4%[Herpes simplex encephalitis](#)9%

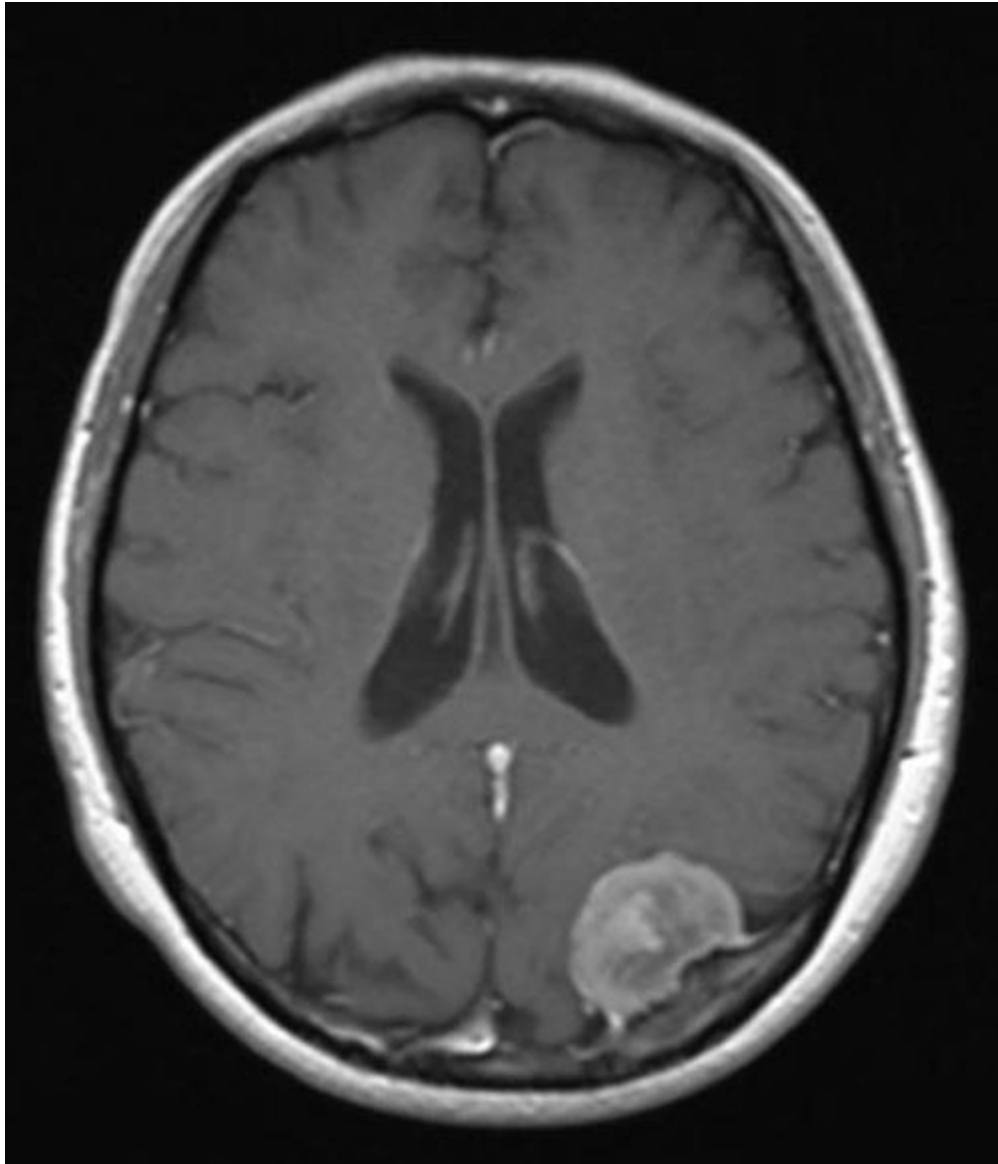
The CT scan shows a left middle frontal gyrus glioblastoma multiforme. Note the peripherally enhancing nature of the lesion, which is a typical feature of a glioblastoma multiforme.

## Brain tumours

The majority of adult tumours are supratentorial, whereas the majority of childhood tumours are infratentorial.

Type of tumour	Features
Glioblastoma multiforme	<ul style="list-style-type: none"> <li>• The most common primary brain tumour in adults.</li> <li>• Histology: Pleomorphic tumour cells border necrotic areas</li> </ul>
Meningioma	<ul style="list-style-type: none"> <li>• The second most common primary brain tumour in adults</li> <li>• Histology: Spindle cells in concentric whorls and calcified psammoma bodies</li> </ul>
Schwannoma	<ul style="list-style-type: none"> <li>• Often seen in the cerebellopontine angle: acoustic neuroma</li> <li>• Bilateral schwannomas are seen in neurofibromatosis</li> <li>• Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)</li> </ul>
Pilocytic astrocytoma	<ul style="list-style-type: none"> <li>• The most common primary brain tumour in children</li> <li>• Histology: Rosenthal fibres (corkscrew eosinophilic bundle)</li> </ul>
Medulloblastoma	<ul style="list-style-type: none"> <li>• More common in children</li> <li>• Found exclusively in the posterior fossa</li> <li>• Metastases through the CSF</li> <li>• Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures</li> </ul>
Ependymoma	<ul style="list-style-type: none"> <li>• Commonly seen in the 4th ventricle</li> <li>• May cause hydrocephalus</li> <li>• Histology: perivascular pseudorosettes</li> </ul>
Oligodendroma	<ul style="list-style-type: none"> <li>• Benign, slow-growing tumour common in the frontal lobes</li> <li>• Histology: Calcifications with 'fried-egg' appearance</li> </ul>

Type of tumour	Features
Haemangioblastoma	<ul style="list-style-type: none"> <li>• Vascular tumour of the cerebellum</li> <li>• Associated with von Hippel-Lindau syndrome</li> <li>• Histology: foam cells and high vascularity</li> </ul>
Pituitary adenoma	<ul style="list-style-type: none"> <li>• Most common type is a prolactinoma</li> <li>• May present with bitemporal hemianopia</li> </ul>
Craniopharyngioma	<ul style="list-style-type: none"> <li>• Most common paediatric supratentorial tumour</li> <li>• Histology: Derived from remnants of Rathke pouch</li> </ul>
Metastases	<ul style="list-style-type: none"> <li>• Most common type of brain tumour</li> </ul>



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**Meningioma** - MRI showing the typical well-circumscribed appearance. A dural tail can be where the tumour 'connects' to the dura. It is seen in around 65% of meningiomas.





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**Glioblastoma multiforme** - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the more homogenous meningioma above.

#### Question 4 of 95

A 58-year-old male is brought into your outpatient clinic by his wife. The patient does not understand why he needs to see a doctor and just wants to get back to work. However, she reports a rather vague history of increasing withdrawal from social interactions and odd repetition of 'catch phrases' over the past 9 months. In addition, she feels his behaviour has changed and is very inappropriate when meeting up with friends, once urinating at the table while having dinner. Last week, he gave her a grave headstone for her birthday, saying 'it is nice to be well-prepared!' While she was understandably upset, he was mystified as to why his well thought out gift might have caused distress. On examination, he continues to repeat the phrase 'Whats up doc?!' at a regular interval, disturbing your history taking. You finally complete a mini-mental test examination, scoring 27/30. What is the most likely diagnosis?

No medical diagnosis 5% Borderline personality disorder 9% Bipolar disorder 6% Schizophrenia 7% Frontotemporal dementia 72%

The history described of behavioural change, lack of insight, mental rigidity and stereotyped behaviours. The prominent behavioural features with a lack of amnesic features are typical for the behavioural variant of frontotemporal dementia. These patients do not typically retain insight and cognitive functions may be normal in early disease. The main differential diagnoses consist of psychiatric disorders. The patient presents with first symptoms at late-fifties and while not impossible, it is rare for psychiatric disorders to be diagnosed so late in life. It is important to rule out other organic causes of behavioural changes with MRI neuroimaging, such as frontal lobe space occupying lesions.

### **Frontotemporal lobar degeneration**

Frontotemporal lobar degeneration (FTLD) is the third most common type of cortical dementia after Alzheimer's and Lewy body dementia.

There are three recognised types of FTLD

- Frontotemporal dementia (Pick's disease)
- Progressive non fluent aphasia (chronic progressive aphasia, CPA)
- Semantic dementia

### **Common features of frontotemporal lobar dementias**

Onset before 65

Insidious onset

Relatively preserved memory and visuospatial skills

Personality change and social conduct problems

### **Pick's disease**

This is the most common type and is characterised by personality change and impaired social conduct. Other common features include hyperorality, disinhibition, increased appetite, and perseveration behaviours.

Focal gyral atrophy with a knife-blade appearance is characteristic of Pick's disease.

Macroscopic changes seen in Pick's disease include:-

- Atrophy of the frontal and temporal lobes

Microscopic changes include:-

- Pick bodies - spherical aggregations of tau protein (silver-staining)
- Gliosis
- Neurofibrillary tangles
- Senile plaques

## CPA

Here the chief factor is non fluent speech. They make short utterances that are agrammatic. Comprehension is relatively preserved.

## Semantic dementia

Here the patient has a fluent progressive aphasia. The speech is fluent but empty and conveys little meaning. Unlike in Alzheimer's memory is better for recent rather than remote events.

## Question 7 of 95

An 18-year-old man presents to your follow-up clinic after the first episode of generalised tonic-clonic seizures, witnessed by his mother lasting for 4 minutes, involving all 4 limbs, before spontaneously terminating. He was initially referred to a first fit clinic and underwent an EEG and MRI, neither of which demonstrated any significant abnormalities. He has now returned to discuss his results and further treatment. The patient and his family realise that there are many ways to manage seizures and are happy to take your recommendation. What is the most appropriate management?

[No treatment66% Sodium valproate16% Lamotrigine6% Levetiracetam6% Carbamazepine5%](#)

Treatment is not usually recommended after a single seizure, as this may have been a provoked seizure instead of the first presentation of epilepsy. One prospective, but methodologically flawed, study demonstrated a 14% risk of seizure recurrent after a single, unprovoked seizure at 1 year<sup>1</sup>. However, the risks significant increase after a patient has had two seizures, rising to 73% recurrent rate at 4 years<sup>2</sup>. It is therefore accepted that antiepileptic treatments should only be commenced after 2 seizures, except if the risks of a further seizure is unacceptable to the patient, an underlying structural defect is proven to be the likely cause of the seizure or if the EEG demonstrated epileptiform activity.

1. Hauser WA, Rich SS, Annegers JF et al. Seizure recurrent after a 1st unprovoked seizure: an extended follow-up. Neurology 1990; 40(8):1163
2. Hauser WA, Rich SS, Lee JR et al. Risk of recurrent seizures after two unprovoked seizures. NEJM 1998; 338 (7):429

## **Epilepsy: treatment**

Most neurologists now start antiepileptics following a second epileptic seizure. NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:

- the patient has a neurological deficit
- brain imaging shows a structural abnormality
- the EEG shows unequivocal epileptic activity
- the patient or their family or carers consider the risk of having a further seizure unacceptable

Sodium valproate is considered the first line treatment for patients with generalised seizures with carbamazepine used for partial seizures

Generalised tonic-clonic seizures

- sodium valproate
- second line: lamotrigine, carbamazepine

Absence seizures\* (Petit mal)

- sodium valproate or ethosuximide
- sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy

Myoclonic seizures

- sodium valproate
- second line: clonazepam, lamotrigine

Focal\*\* seizures

- carbamazepine or lamotrigine
- second line: levetiracetam, oxcarbazepine or sodium valproate

\*carbamazepine may actually exacerbate absence seizure

\*\* the preferred term for partial seizures

#### Question 1 of 87

A 42-year-old man attends the GP reporting hearing loss. He reports sudden-onset right hearing loss that has remained continuous for the past three weeks. He notes that the day prior to this he hit his head with some force. Additionally, he mentions he has been experiencing some dizzy episodes over the same time frame. He goes onto have a pure-tone audiogram that demonstrates significant sensorineural hearing loss on the right side.

What is the most likely diagnosis?

[Stroke19%](#)[Benign paroxysmal positional vertigo \(BPPV\)5%](#)[Meniere's disease21%](#)[Acoustic neuroma20%](#)[Subdural haemorrhage35%](#)

The sudden onset of symptoms points towards a stroke. Specifically, this is a labyrinthine infarction. The head trauma (which may be quite trivial) can cause a dissection of the vessel (typically the anterior cerebellar artery) supplying the labyrinthine artery. This produces an embolism resulting in ischaemia of the labyrinthine, producing the above symptoms. Thus, it is important to consider this diagnosis in a patient presenting with sudden-onset unilateral hearing loss.

BPPV would not typically affect hearing.

Acoustic neuroma and Meniere's disease would not result in sudden-onset symptoms.

Subdural haemorrhage tends to affect an older age group, with presenting features usually related to altered conscious level and headache.

#### Question 2 of 87

A 48-year-old woman presented to the emergency department with a severe headache. Symptoms had started early that day while the patient had been walking around her office with the headache reaching maximal intensity within a few minutes. The pain was felt across the entirety of the patient's head and was much improved when she lay down flat. There were no associated symptoms and the patient had been constitutionally well in the preceding days.

The patient had no past medical history and was nulliparous. She was a non-smoker who consumed 15 units of alcohol per week.

Clinical examination demonstrated no evidence of focal neurological deficit and no signs of meningism. Simple analgesia given in the emergency department had limited impact on the patient's headache.

CT brain with venogram: no evidence of intra-axial or extra-axial bleeding; no space occupying lesion; no hydrocephalus; no evidence of venous sinus thrombosis

Lumbar puncture: opening pressure 5 mmHg; red cells 8 mm<sup>3</sup>; white cells 1 / mm<sup>3</sup>; no xanthochromia

What is the next best investigation to confirm the likely diagnosis?

[Digital subtraction myelography14% Cerebral angiography33% CT brain with contrast7% MRI whole spine with STIR11% MRI brain with gadolinium35%](#)

The clinical presentation and initial investigations are suggestive of spontaneous intracranial hypotension. The key aspect of the history is the strong postural relationship to pain with the headache worsening within a few seconds of upright posture and easing within a minute of lying horizontal. Spontaneous intracranial hypotension can cause either a headache of insidious or rapid onset. A low opening pressure on lumbar puncture (< 6 cmCSF) is one of the diagnostic criteria.

Diagnosis is confirmed by MRI with gadolinium that demonstrates distinctive dural gadolinium enhancement and downward displacement of brain on sagittal views.

In some cases of spontaneous intracranial hypotension, investigations such as MRI whole spine with STIR sequences or digital subtraction myelography may be used to identify the location of CSF leak in order to guide blood patch treatment.

Scott S, Davenport R. Low pressure headaches caused by spontaneous intracranial hypotension. BMJ 2014;349:6219.

## **Spontaneous intracranial hypotension**

Spontaneous intracranial hypotension is a very rare cause of headaches that results from a CSF leak. The leak is typically from the thoracic nerve root sleeves.

Risk factors include connective tissue disorders such as Marfan's syndrome.

#### Key features

- strong postural relationship with the headache generally much worse when upright. Patients may, therefore, be bed-bound

#### Investigations

- MRI with gadolinium: typically shows pachymeningeal enhancement

#### Management

- usually conservative
- if this fails an epidural blood patch may be tried

#### Question 3 of 87

A 35-year-old lady with no significant past medical history presents to you with lethargy and fatigue over several years, often finding she does not sleep well at night. She complains of a sensation of discomfort in her lower extremities at rest, particularly worse when she is trying to fall asleep. She also describes an abnormal crawling and itching sensation below the knees and often walking will relieve her symptoms. There is no history of pain or night time snoring. Clinical examination and routine blood investigations are unremarkable. She tells you that over the years her general practitioner has ordered several tests on her that have all been normal, including brain imaging, thyroid function, and monitoring of her haemoglobin levels. She is not on any medications. She is now struggling to do her job as a teacher and is now working only part time because of the symptoms. Considering the likely underlying diagnosis, which of the following would you use to try and alleviate her symptoms?

[Lithium5%Quinine19%Pramipexole47%Amitriptyline24%Acetazolamide5%](#)

The diagnosis is restless leg syndrome (RLS). This is a neurologic movement disorder of the limbs that is often associated with a sleep complaint. This will often end up presenting in neurology clinics and it is important to know how to help such patients. RLS can lead to significant physical and emotional disability.

Specific DSM-5 criteria for RLS are as follows:

- an urge to move the legs that is usually accompanied by or occurs in response to uncomfortable and unpleasant sensations in the legs, characterized by all of the following: (1) the urge to move the legs begins or worsens during periods of rest or inactivity; (2) the urge is partially or totally relieved by movement; and (3) the urge to move legs is worse in the evening or at night than during the day or occurs only in the evening or at night.
- Symptoms occur at least 3 times per week and have persisted for at least 3 months.
- Symptoms cause significant distress or impairment in social, occupational, educational, academic, behavioural or other areas of functioning.
- The symptoms cannot be attributed to another mental disorder or medical condition (e.g., leg oedema, arthritis, leg cramps) or behavioural condition (e.g. positional discomfort, habitual foot tapping)
- The disturbance cannot be explained by the effects of a drug of abuse or medication

85% of patients with RLS have periodic movements of sleep, usually involving the legs (periodic leg movements of sleep [PLMS]). This is characterised by involuntary, forceful dorsiflexion of the foot lasting 0.5-5 seconds and occurring every 20-40 seconds throughout sleep. It is, therefore, worth taking a collateral history from a partner if available.

Investigations should include excluding iron deficiency (which may potentiate RLS) and you should order sleep studies to characterise the extent of sleep disturbance.

First line drug treatments are dopaminergic agents (eg, pramipexole, ropinirole, bromocriptine, levodopa-carbidopa, and rotigotine) or gabapentin/pregabalin. Nonpharmacologic approaches include exercise, avoidance of caffeine, alcohol, and nicotine. Also important to try and stop medications that exacerbate RLS if possible, eg selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), diphenhydramine, and dopamine antagonists.

## **Restless legs syndrome**

Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia. It is extremely common, affecting between 2-10% of the general population. Males and females are equally affected and a family history may be present

Clinical features



- uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day. Symptoms are worse at rest
- paraesthesias e.g. 'crawling' or 'throbbing' sensations
- movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)

#### Causes and associations

- there is a positive family history in 50% of patients with idiopathic RLS
- iron deficiency anaemia
- uraemia
- diabetes mellitus
- pregnancy

The diagnosis is clinical although bloods to exclude iron deficiency anaemia may be appropriate

#### Management

- simple measures: walking, stretching, massaging affected limbs
- treat any iron deficiency
- dopamine agonists are first-line treatment (e.g. Pramipexole, ropinirole)
- benzodiazepines
- gabapentin

#### Question 1 of 84

A 37-year-old woman has been diagnosed with relapsing remitting multiple sclerosis and is considering further therapeutic options including natalizumab. She has had two severe relapses despite treatment with glatiramer acetate. She is currently still able to work, but is very fatigued and feels her mobility is limited.

On examination, she has brisk reflexes bilaterally, with mild weakness in her proximal left leg and reduced sensation in the left foot.

She has highly active disease on her brain MRI with multiple acute and sub-acute plaques present. She also has a single lower cervical cord lesion.

Before considering a new therapy, aside from HIV and general immunological status, which of the following investigation results is of greatest importance?

Cytomegalovirus status 10% Syphilis serology 5% Hepatitis C serology 7% EBV serology 5% JC virus status 73%

Natalizumab is a therapy approved for the management of highly active relapsing-remitting multiple sclerosis (RRMS) and is given as a once-monthly infusion. Natalizumab has been shown to greatly reduce relapse rates in RRMS.

It is a humanised monoclonal antibody against the cell adhesion molecule (CAM) 4-integrin. Natalizumab prevents leukocyte adhesion to endothelial VCAM1, thus preventing the migration of immune cells into the CNS.

An extremely rare, severe and almost universally fatal adverse side effect of Natalizumab is progressive multifocal leukoencephalopathy (PML). Only patients who are seropositive for JC virus are at risk of developing PML with exposure to natalizumab, and therefore checking the JC virus status of patients who are considering natalizumab therapy is mandatory.

It is also worth noting that some patients with low titres of JC virus are still commenced on natalizumab under close monitoring and that duration of natalizumab therapy is proportional to the risk of developing PML, i.e. short duration therapy (1-2 years) carries a very low risk of developing PML, even in those with a low positive JC virus titre. Ultimately, patients who are JC virus positive should not receive natalizumab and another therapy should be considered.

## **Multiple sclerosis: management**

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

### **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

### **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

### **Some specific problems**

#### Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

#### Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

#### Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

#### Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line

#### Question 4 of 84

A 35-year-old man is brought into the Emergency Department after 3 successive tonic-clonic seizures. He was given 10mg of rectal diazepam and has since stabilised.

A brief history from his girlfriend states that he was usually fit and well apparent from recurrent sinusitis. Over the past month, however, he had been complaining of increasing headaches and had received a course of antibiotics from his GP.

He takes no regular medication but his partner states that they do occasionally take ecstasy whilst on nights out.

On examination, he is drowsy with a Glasgow Coma Scale (GCS) of 12. His temperature is 38.8 degrees Celsius, his pulse is 57 bpm and regular, blood pressure 150/90 mmHg, oxygen saturations 97% on 15L oxygen via a non-rebreathe mask.

Cardiovascular examination reveals normal heart sounds, capillary refill time of 3 seconds. His calves were soft and non-tender. His chest was clear with no signs of consolidation. Abdominal examination was unremarkable.

Neurological examination was difficult in view of the patients low GCS but no focal abnormality could be detected. On attempt to passively flex his neck he became agitated and obviously uncomfortable. Pupils were equal and reactive to light. Fundoscopy demonstrated bilateral oedematous optic discs.

Bloods were as follows:

Na+ 130 mmol/L

K+ 3.9 mmol/L

Urea 5 mmol/L

Creatinine 80  $\mu$ mol/L

Hb 160 g/L

WBC  $25.0 \times 10^9$ /L

Neutrophils 91%

LFTs Normal

CRP 90 mg/L

Based on the findings above, what is the most likely diagnosis?

[Intracerebral abscess](#)50%[Sepsis secondary to sinusitis](#)7%[Ecstasy overdose](#)7%[Meningitis](#)31%[Cerebral lymphoma](#)6%

This is a 30-year-old man who presented with a history of headaches, seizures and a fever. The history of headaches and a course of antibiotics could suggest partially treated sinusitis. This has likely extended posteriorly resulting in an intracranial abscess as indicated by the inflammatory markers, signs of raised intracranial pressure and seizures.

Meningitis can sometimes present with seizures if this has progressed to meningoencephalitis but the history of recurrent sinusitis and headaches with raised intracranial pressure are more suggestive of a space occupying abscess.

Although ecstasy overdose can cause pyrexia and seizures, it is not in keeping with the chronic progression of this patient's symptoms.

Seizures have been associated with severe sepsis but it is not in keeping with all of the signs and symptoms demonstrated here.

## **Intracerebral abscess**

### Features

- fever
- headache
- seizures
- signs of raised intracranial pressure
- focal neurological deficits

### Management

- surgical drainage: supratentorial abscesses may be drained via a burr hole
- antibiotic therapy



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CT demonstrating a cerebral abscess. CT demonstrates a rounded lesions with vast amounts of surrounding vasogenic oedema resulting in mass effect and distortion of the cerebral peduncle. Contrast confirms the presence of a smooth ring of enhancement, characteristic of an abscess.

#### Question 5 of 84

A 42 year-old man presents with an acute onset of weakness in the left face, arm, and leg, which has not resolved. On examination there is upper motor neuron facial weakness on the left, with dense weakness of the left arm and leg. There is no evidence of sensory neglect, hemianopia, or dysphasia.

His past medical history includes migraine with visual aura, for which he takes propranolol and sumatriptan. His last migraine attack was a month ago. He has suffered two transient ischaemic attacks in the last year, and now also takes clopidogrel. His father also suffered from migraine

with aura and died in his 50s after suffering a series of strokes.

Plain computed tomography shows multiple round lesions in the white matter, which appear the same density as cerebrospinal fluid. Magnetic resonance imaging shows scattered well-circumscribed lesions in the subcortical white matter which appear hypointense on T1 and hyperintense on T2-weighted sequences. On DWI (diffusion-weighted imaging) there is a hyperintense lesion in the right internal capsule, with a corresponding hypointense area on the ADC (apparent diffusion coefficient) map.

What is the most likely underlying diagnosis?

[Patent foramen ovale7%Progressive multifocal leukoencephalopathy14%Migrainous infarction11%Cerebral amyloid angiopathy15%CADASIL53%](#)

The clinical and radiological description fits with a lacunar infarction in the right internal capsule resulting in a pure motor hemiparesis. The area of acute infarction is not visible on the CT in the hyperacute phase, but is visible on the diffusion-weighted MR as described. The other white matter lesions are most likely old lacunar infarcts which may have been clinically silent.

The personal history of migraine with aura coupled with the family history make this most likely CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). The condition results from mutations in the NOTCH3 gene on chromosome 19. Individuals typically develop migraine with aura around age 30, transient ischaemic attacks and ischaemic strokes in their 40s, and dementia around the 50s. Strokes are typically lacunar.

There is an association between patent foramen ovale, migraine with aura, and stroke. Stroke in this context is embolic, which characteristically produces wedge-shaped infarcts involving cortex and white matter, rather than the small lesions seen in lacunar stroke. Emboli may arise in the venous circulation and cross over into the arterial circulation via the shunt (paradoxical embolism).

Progressive multifocal leukoencephalopathy is a demyelinating disease of the central nervous system caused by reactivation of the JC virus, most typically seen in patients with AIDS and low CD4 counts.

In migrainous infarction the neurological deficit develops during an attack of migraine.

Cerebral amyloid angiopathy is an important cause of primary lobar intracerebral haemorrhage in the elderly.

## **CADASIL**

## Overview

- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
- rare cause of multi-infarct dementia
- patients often present with migraine

### Question 6 of 84

A 69-year-old retired accountant was seen in the neurology clinic having been referred by his GP. He presented with a three-month history of malaise and weakness. The weakness initially affected his legs, and at times he felt that his legs would not support him standing up. Over the course of the last month, however, he also noticed weakness in his hands, especially his left hand. This was particularly noticeable when he rode his motorbike when he felt that his fingers were not strong enough to apply the brakes. In addition, his wife remarked that his speech had changed in tone though he did not have any difficulties with understanding or expressing speech. His past medical history comprised hypertension, hypercholesterolaemia, depression and hypothyroidism. His medication regimen included amlodipine 5mg OD, atorvastatin 20mg ON, citalopram 20mg OD and levothyroxine 125mcg OD. He also remarked that he had been referred by his GP to the fast track gastroscopy clinic and was pending an appointment for new onset difficulty in swallowing food over the last month. He did not smoke and did not consume alcohol. Upon a systems review, he denied the presence of other symptoms though he did admit to losing 3kg of weight since the onset of his symptoms.

On examination, he appeared cachectic with obvious dysarthria. His blood pressure was 128/78 mmHg and his heart rate was 78bpm. Examination of his cranial nerves revealed the presence of tongue fasciculations with tremulous lips and an absent jaw jerk reflex but was otherwise unremarkable. Examination of his peripheral nervous system revealed small muscle intrinsic wasting of both hands, as well as wasting of his thigh muscles. The tone was reduced in his lower limbs but increased in his upper limbs. He had obvious weakness of all muscle groups, with a grade 4/5 weakness in his lower limbs and proximal upper limb and a grade 3/5 weakness in his distal upper limbs. Fasciculations were present in his thighs and forearms. Both upper and lower limb reflexes were brisk with downgoing plantars. Examination of sensation was normal. Examination of the cardiovascular, respiratory and gastrointestinal systems was unremarkable.

Investigations conducted by the GP prior to referral are as follows:

Hb	111 g/l
Platelets	$99 \times 10^9/l$
WBC	$12.2 \times 10^9/l$
ESR	18 mm/hr



CRP                      6 mg/l  
ANA                     positive  
Rheumatoid factor negative

Which one of the following interventions is most likely to be of benefit?

[Mitoxantrone7%Riluzole74%Rivastigmine8%Methotrexate5%Azathioprine6%](#)

This patient has motor neurone disease (MND), with clinical evidence of amyotrophic lateral sclerosis and bulbar palsy. Of the above options only riluzole, an anti-glutamate, has been shown to be of any benefit and is suitable for the amyotrophic lateral sclerosis variant of MND. The presence of ANA antibodies is a red herring; it is thought to be present in up to 15% of healthy individuals and is not associated with MND.

### **Motor neuron disease: management**

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

#### Riluzole

- prevents stimulation of glutamate receptors
- used mainly in amyotrophic lateral sclerosis
- prolongs life by about 3 months

#### Respiratory care

- non-invasive ventilation (usually BIPAP) is used at night
- studies have shown a survival benefit of around 7 months

#### Prognosis

- poor: 50% of patients die within 3 years

### Question 7 of 84

A 74-year-old female has been diagnosed with moderate to severe Alzheimer's disease, on a background of a two-year progressive gradual cognitive decline. Her family had tried to cope on their own without seeking medical help, putting it down to old age but now, most likely requires nursing home care. MMSE 7/30. She has a past medical history of previous myocardial infarctions. She has not complained of chest pain recently and her ECG demonstrates no ischaemic changes, a PR interval of 290ms. What is the most appropriate treatment strategy?

[Donepezil24%](#) [Memantine48%](#) [Galantamine8%](#) [Rivastigmine13%](#) [Aspirin7%](#)

There are two key facts to this patient: firstly, the patients MMSE is suggestive of severe dementia. Secondly, the diagnosis of 1st degree heart block and hence atrioventricular nodal block is a contraindication for cholinesterase inhibitors, which could precipitate complete heart block. In accordance with the latest set of NICE guidelines, donepezil, galantamine and rivastigmine are all appropriate for mild to moderate dementia, defined as MMSE between 10 and 26/30. However, only memantine, an NMDA antagonist, has demonstrated efficacy and is licensed for severe Alzheimer's disease.

## Alzheimer's disease

Alzheimer's disease is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK

### Genetics

- most cases are sporadic
- 5% of cases are inherited as an autosomal dominant trait
- mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- apolipoprotein E allele E4 - encodes a cholesterol transport protein

### Pathological changes

- macroscopic: widespread cerebral atrophy, particularly involving the cortex and hippocampus
- microscopic: cortical plaques due to deposition of type A-Beta-amyloid protein and intraneuronal neurofibrillary tangles caused by abnormal aggregation of the tau protein

- biochemical: there is a deficit of acetylcholine from damage to an ascending forebrain projection

### Neurofibrillary tangles

- paired helical filaments are partly made from a protein called tau
- in AD tau proteins are excessively phosphorylated

### Management

- NICE now recommend the three acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease
- memantine (a NMDA receptor antagonist) is reserved for patients with moderate - severe Alzheimer's

### Question 9 of 84

A 42-year-old woman presents with 6 days of drowsiness and a gradual onset headache, initially starting in the occipital region and radiating to the apex. She has recently returned from Australia in holiday one week ago but has complained of poor appetite after a cough and cold since landing. She has no past medical history, takes no regular medications except the oral contraceptive pill. She is a non-smoker and drinks minimally. On examination, the patient has a full range of neck movements and no photophobia. Examination of her limbs is unremarkable. You request a CT head without contrast, which demonstrates two small areas of subarachnoid blood in right convexity. She denies any recent head trauma. Which investigation will most likely provide the conclusive diagnosis?

[CT head with contrast](#)5% [MRI head](#)7% [MR venogram](#)45% [Lumbar puncture with xanthochromia](#)18% [CT angiography](#)25%

The patient presents with a non-specific headache on a background of a number of different risk factors for venous thromboembolic disease: recent long-haul flight, likely dehydration from poor oral intake, oral contraceptive pill. A generalised headache is present in almost 90% of all patients with cerebral venous thrombosis (CVT)<sup>1</sup>. The headache is caused by impaired absorption of cerebrospinal fluid due to the sinus thrombus, resulting in increased intracranial pressure. CVTs can also present with seizures, encephalopathy and focal symptoms, but be aware that the presenting clinical features can be extremely variable.

A plain CT head can sometimes demonstrate signs of CVT in one-third of patients. A dense triangle sign is often seen in the posterior superior sagittal sinus. In addition, the empty or negative delta sign<sup>2</sup>, is

seen on a contrasted CT head where a central area is lacking contrast flow due to thrombus obstruction. However, MR venogram (CT venogram in the hands of highly skilled radiologists) is the most sensitive imaging modality.

This scenario is a useful demonstration that not all subarachnoid blood equates to a spontaneously ruptured aneurysm. Cerebral venous thrombosis is a classic cause of intraparenchymal and subarachnoid haemorrhages, particularly if around the convexity<sup>3</sup>. In addition, the description of the headache is atypical for an aneurysmal subarachnoid haemorrhage: the headache is of gradual onset, persists for days, with no meningism. Although it may seem illogical, treatment with anticoagulation will treat the sinus thrombus, resulting in improved CSF flow, while the subarachnoid blood will slowly resolve.

1. Ferro JM, Canhão P, Stam J et al. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664
2. Lee EJ. The empty delta sign. *Radiology*. 2002;224(3):788
3. Sztajzel R, Coeytaux A, Dehdashti AR et al. Subarachnoid hemorrhage: a rare presentation of cerebral venous thrombosis. *Headache*. 2001;41(9):889

## **Intracranial venous thrombosis**

### **Overview**

- can cause cerebral infarction, much less common than arterial causes
- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

### **Features**

- headache (may be sudden onset)
- nausea & vomiting

### **Sagittal sinus thrombosis**

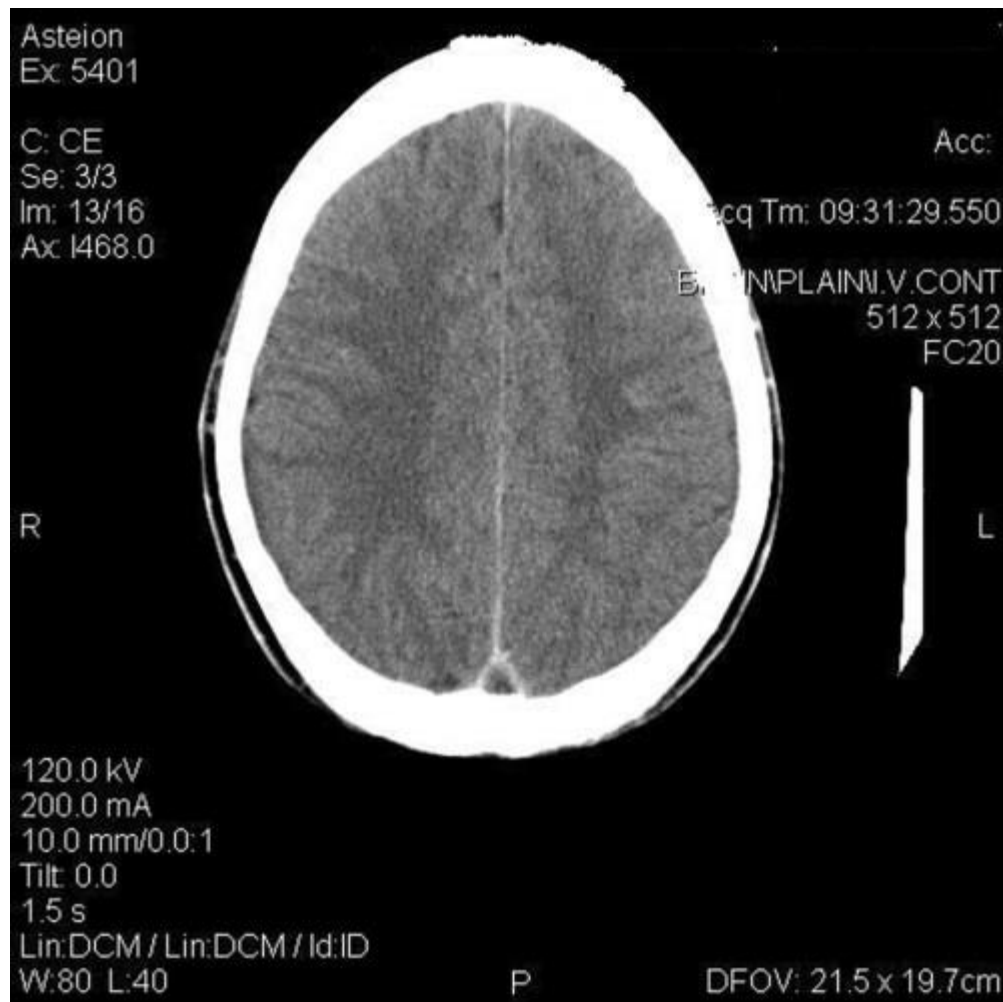
- may present with seizures and hemiplegia
- parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

### Cavernous sinus thrombosis

- other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

### Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies



CT with contrast demonstrating a **superior sagittal sinus thrombosis** showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

#### Question 10 of 84

A 44-year-old male presents to your headache clinic with a 6-month history of left-sided daily headaches located in the frontal and retroorbital area. He denies any pain-free periods. The headaches are of moderate 5/10 severity with unpredictable exacerbations of severe pain going up to 9/10 severity. He describes to you what sounds to you like left-sided conjunctival injection and lacrimation often occurring alongside the headaches. Which of the following is most likely to aid you in making a diagnosis?

[a trial of high flow 100% oxygen41%Lumbar puncture5%a trial of indomethacin40%CT brain6%MRI brain8%](#)

A headache with absolutely no pain-free periods otherwise described like this (i.e. like a trigeminal autonomic cephalalgia (TAC)) is hemicrania continua.

The trigeminal autonomic cephalalgias should be side-locked (i.e. one side only) and typically but not exclusively in the retroorbital/temporal region. They should include some autonomic parasympathetic feature such as eye-watering, red eye, running nose, a sensation of fullness in the ear, or miosis. These should be ipsilateral to the pain. They are a spectrum and most conveniently differentiated by how long the headache lasts for and how frequent the attacks happen per day. Some features are quite noticeable in TAC, e.g in a cluster headache (aka 'suicide headaches') people are usually very animated and pace about/hold their head in pain/want to smash their head against the wall (contrast this to migraine: which is not a TAC and usually involves sitting still in a dark room and not making any noise).

It is worth looking up the International Classification of Headache Disorders diagnostic criteria for TACs. Here are some important features:

- Cluster headaches: attacks have a frequency between one every other day and 8 per day and last 15-180 minutes.
- Paroxysmal hemicrania: attacks have a frequency above five per day and last 2-30 min. The condition responds absolutely to indomethacin
- Hemicrania continua: a constant form of paroxysmal hemicrania (no headache-free periods). Also responds absolutely to indomethacin.

- Short-lasting unilateral neuralgiform headache attacks: could get 20 attacks in a day, each last around 1600 seconds.

Notice the differences between how long each lasts and how many attacks there can be per day. The rest of the features are quite similar to each other between the headaches, so learn the general features of a TAC then memorise how long each should last and its frequency to help you differentiate them.

Returning to the question: hemicrania continua and paroxysmal hemicrania clearly are the two that completely resolve with indomethacin. The history, therefore, helps differentiate which is which. Practically speaking, you bring these patients in, on two separate days, for a trial injection of indomethacin or placebo (water) where patient (and nurse if possible) is blinded to which is which and we see which one of the two days was associated with resolution of headaches at a later date in clinic (give the patient a headache diary to take home with). Note the 100% oxygen trial would be used for cluster headaches, which tends to respond to this.

Ref: <https://www.ichd-3.org/3-trigeminal-autonomic-cephalalgias/>

## **Trigeminal autonomic cephalalgias**

Trigeminal autonomic cephalalgias (TACs)

- cluster headache
- paroxysmal hemicrania
- hemicrania continua
- short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome)
- short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)

Question 1 of 74

A 27 year old lady with relapsing-remitting multiple sclerosis (MS) is referred to your clinic. She was diagnosed at age 18 and has been managed on interferon  $\beta$  1a, with only four relapses in her total history. She has made good recovery from all four relapses and the only finding on neurological examination is of mild dysdiadochokinesis of the left arm. She scores functionally very well on an expanded disability status scale (EDSS) and has no disability as a result.

She is planning her first pregnancy and wanted advice on how her MS may be affected. She has already been advised on stopping interferon  $\beta$  1a in preparation for pregnancy. Aside from the impact of stopping interferon  $\beta$  1a, she wants to know how pregnancy itself will affect her MS. Which of the following is most accurate?

Relapse rates may decrease during pregnancy, increase at 3-6 months post-partum then return to pre-pregnancy rates.55% There is an increased risk of developing visual disorders associated with MS. 7% There is a 30% chance that her RRMS will evolve into progressive MS. 9% There is a 15% chance that her relapse rate will decrease for the five years following pregnancy.8% Relapse rates may increase during pregnancy, then return to pre-pregnancy rates at 9 months post-partum.22%

A knowledge of the issues surrounding pregnancy in MS is important, since females of a child-bearing age are a high risk group for developing the disease.

NICE guidance states that 'relapse rates may reduce during pregnancy and may increase 3 to 6 months after childbirth before returning to pre-pregnancy rates'. It also states that pregnancy does not increase the risk of progression of disease; the net effect of protection during pregnancy and subsequent increased relapse rate carries no increased risk of exacerbation.

With regard to Interferon  $\beta$  1a in pregnancy, most neurologists would advise stopping when pregnancy is considered, due to inconsistent and conflicting data in the area. The BNF advises against use in pregnancy 'unless potential benefit outweighs risk'.

If a person with MS is thinking about pregnancy, they must have the opportunity to talk with a healthcare professional with knowledge of MS about:

- fertility
- the risk of the child developing MS
- use of vitamin D before conception and during pregnancy
- medication use in pregnancy
- pain relief during delivery (including epidurals)
- care of the child
- breastfeeding.

In this scenario the use of the expanded disability status scale (EDSS) was referred to. This provides an index of clinical disability and may be used to quantify disease progression. It has widespread use in clinical trials.

NICE guidance: multiple sclerosis

<http://pathways.nice.org.uk/pathways/multiple-sclerosis/managing-multiple-sclerosis#content=view-node:nodes-provide-information-and-support>

BNF: Interferon Beta.



Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33:1444.

## **Multiple sclerosis: management**

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

### **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

### **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

## **Some specific problems**

### **Fatigue**

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine

- other options include mindfulness training and CBT

### Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

### Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying  
- anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

### Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line

### Question 2 of 74

A 68-year-old female presents via blue light ambulance to the emergency department with a first seizure, witnessed by her husband. He describes a sudden onset limb jerking lasting for around 6 minutes, associated with urinary incontinence and tongue biting, with a period of confusion and drowsiness immediately after. He is not aware of her having had any previous seizures, she has no other past medical history and does not take drugs on a medical history. He, however, does describe her to be 'not quite herself' over the past four weeks when she appears to have been extremely agitated and occasionally extremely paranoid. He had thought it to be linked to her not feeling very well, during a period when she had complained of a 'flu-like' headache, generalised muscle ache and a non-productive cough.

You examine her, finding significant gait and limb ataxia with no truncal ataxia. Her blood tests are unremarkable except for positive anti-NMDA antibodies. Her MRI scan demonstrates swelling in bilateral limbic cortices and other no other intracranial abnormalities. She has declined a lumbar puncture and is thought to retain capacity.

Which investigation would most likely provide the underlying diagnosis?

[CT abdomen/pelvis with contrast39%](#)[Lumbar puncture18%](#)[Nerve conduction studies and EMG18%](#)[MRI spine15%](#)[Muscle biopsy10%](#)

This middle aged woman has presented with seizures on a background of personality change, agitation, paranoia and cerebellar ataxia. The diagnostic test is her positive anti-NMDA antibody, with MRI confirm limbic encephalitis as a result of a paraneoplastic syndrome. The underlying diagnosis is classically an ovarian teratoma, presenting antigens to the body's immune system similar to the brain limbic areas, driving an immune-related encephalitis. Treatment requires immunosuppression with intravenous steroids, immunoglobulin's or plasma exchange, in addition to removal of the underlying tumour by surgery.

### **Anti-NMDA receptor encephalitis**

Anti-NMDA receptor encephalitis is a paraneoplastic syndrome, presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability. Ovarian teratomas are detected in up to half of all female adult patients, particularly prevalent in Afro-Caribbean patients<sup>1</sup>. MRI head can be normal but abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures<sup>2</sup>. CSF may demonstrate pleiocytosis but can be normal initially. Anti-MuSK is an autoantibody specific to muscle kinase in myasthenia gravis with no evidence of a thymoma and without antibodies to acetylcholine receptors. Anti-GM1 is an autoantibody specific to acute inflammatory demyelinating polyneuropathy (AIDP) variant of Guillain-Barre syndrome.

Treatment of anti-NMDA encephalitis is based of immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination. Resection of teratoma is also therapeutic.

### **Question 3 of 74**

A 76-year-old male is referred by the GP to your Parkinson's disease clinic. The patient and his wife described an increasing frequency of falls, the most frightening of which occurred when he fell 4 steps down a flight of stairs last week, luckily with no lasting damage. On examination, you note a slow pill rolling tremor equally on both hands and bilateral cog-wheeling. His cranial nerves are unremarkable except a poverty of upwards gaze. His speech appears distinct and nasal in character. What is the most likely diagnosis?

[Idiopathic Parkinson's disease7%](#) [Vascular parkinsonism6%](#) [Progressive supranuclear palsy \(PSP\)76%](#) [Multi-system atrophy \(MSA\)7%](#) [Corticobasal degeneration \(CBD\)4%](#)

PSP is most likely in this scenario. A number of features should alert you to a Parkinson's-plus syndrome instead of idiopathic Parkinson's disease: bilateral, symmetrical symptoms are uncommon, particularly in early PD. In addition, eye signs are very unusual. PSP patients classically present with increasing falls near the stairs due to an impaired vertical gaze and a nasal 'Donald-Duck' voice secondary to pseudobulbar palsy. MSA patients classically present with significant cerebellar or autonomic symptoms. CBD present with higher order dysfunction such as apraxia and aphasia, but classically with 'alien hand syndrome', thought to be as prevalent as 60% of CBD patients, when the patient has no control over their own hand movements.

## **Progressive supranuclear palsy**

### Overview

- aka Steele-Richardson-Olszewski syndrome
- a 'Parkinson Plus' syndrome

### Features

- impairment of vertical gaze (down gaze worse than up gaze - patients may complain of difficulty reading or descending stairs)
- parkinsonism
- falls
- slurring of speech
- cognitive impairment

### Management

- poor response to L-dopa

A 4-year-old boy with infantile spasms commences treatment with the antiepileptic drug vigabatrin. What monitoring is required of patients commencing vigabatrin therapy?

[Platelets 12%](#)[Liver function test 19%](#)[Visual field examination 55%](#)[Ophthalmoscopy for raised intracranial pressure 9%](#)[Spirometry 6%](#)

Vigabatrin can cause irreversible visual field constriction. A baseline visual field should be obtained before starting treatment. Visual field examination should be undertaken with Humphrey 120 point, Octopus 07, or Goldmann perimetry (III4e and I4e or I2e stimuli, as appropriate). Perimetry should be repeated every 6 months for 5 years and annually thereafter.

A NICE Technology Appraisal in 2004 found that there was no convincing evidence for superiority of seizure control by vigabatrin compared with alternative therapies in either infantile spasms or partial seizures. However, the risk of visual field constriction attributable to vigabatrin must be balanced against the adverse effects of alternative therapies, and of uncontrolled epilepsy and is therefore still licensed for use.

## **Vigabatrin**

### **Key points**

- 40% of patients develop visual field defects, which may be irreversible
- visual fields should be checked every 6 months

### **Question 1 of 69**

Vincent, 28, has treatment resistant schizophrenia, with his usual symptoms being auditory hallucinations and persecutory delusions. He was recently prescribed clozapine, fluoxetine and lactulose. He has been complaining of constipation recently, but now presents to the emergency department with acute abdominal pain and vomiting. On examination abdomen is distended. What is the most likely cause?

[Intestinal obstruction 49%](#)[Appendicitis 6%](#)[Constipation 19%](#)[A bezoar 20%](#)[Ingestion of foreign object 7%](#)

The most likely cause of this patient's presentation is intestinal obstruction. Intestinal obstruction is one of the more under-recognised complications of clozapine therapy, yet one of the more serious. Gastric hypomotility is common in patients who are treated with clozapine, and its

presentation can range from a simple constipation to more severe conditions such as intestinal obstruction, bowel ischaemia and necrosis.

The important pieces of information to consider when answering this question are the recent prescription of clozapine, the presence of constipation previous to current presentation, and his physical presentation of acute abdominal pain and vomiting with distension. When answering a question such as this, recent prescriptions of medications prior to the deterioration of their physical condition should raise the thought that maybe one of the medications is causing the symptoms. In this scenario, the patient has recently been prescribed clozapine, fluoxetine and lactulose. Therefore, considering each of these medications and their side effects is a must.

The patient's presentation, and recent past medical history, provides a good indication of what could be the underlying issue. The patient has presented with acute abdominal pain and vomiting. When you consider this with the recently experienced constipation, it becomes clear that this patient is likely suffering from an obstruction, as opposed to the other options on offer.

Constipation would be an inappropriate answer to this question. Although he has had constipation recently, and abdominal pain could be a presentation of constipation, vomiting is not generally observed in constipation. This would mean that this diagnosis is less likely.

Bezoars are indigestible masses that become trapped in the gastrointestinal tract. They can occur when individuals consume a variety of items, including hair, soil, chewing gum etc. These items form a mass, which ultimately becomes lodged in the gastrointestinal tract, often requiring surgical intervention to relieve the obstruction. The symptoms that the patient in this scenario has experienced could be explained by a bezoar, however, we do not have any evidence that he consumes any items that may lead to a bezoar. Furthermore, the recent commencement of clozapine means that we cannot select a bezoar as the most likely cause of this patient's symptoms above intestinal obstruction. Similarly, we do not have any evidence that the patient ingests foreign objects, meaning that this cannot be classed as a likely cause in this question.

Appendicitis could explain the acute presentation of this patient. However, the fact that the patient experienced constipation prior to him developing acute abdominal pain and vomiting means that appendicitis is less likely.

## **Atypical antipsychotics**

Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines. The main advantage of the atypical agents is a significant reduction in extra-pyramidal side-effects.

Adverse effects of atypical antipsychotics

- weight gain
- clozapine is associated with agranulocytosis (see below)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

Examples of atypical antipsychotics

- clozapine
- olanzapine
- risperidone
- quetiapine
- amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication

Adverse effects of clozapine

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients

Question 2 of 69

A 35-year-old gentleman presents with weakness raising up his arms and some drooping of the eyelids and his shoulder blades are pronounced. He says his symptoms are mild and he probably would not have noticed it except his father had similar symptoms that have steadily got worse. This gentleman has no other past medical history of note and is taking no regular medications. On examination there is mild evidence of scapula winging, proximal weakness of both upper limbs, ptosis and he has difficulty whistling. There is normal power of his lower limbs and reflexes and sensation is intact throughout.

Creatine kinase 220 units/L

A muscle biopsy is sent but is pending, what is the most likely diagnosis?

[Facioscapulohumeral dystrophy69%](#)[Myotonic dystrophy11%](#)[Emery-Dreifuss muscular dystrophy7%](#)[Becker muscular dystrophy7%](#)[Oculopharyngeal muscular dystrophy6%](#)

Facioscapulohumeral dystrophy is usually an autosomal dominant condition and although it affects men and women equally, men may be more symptomatic. Shoulder, upper arm and facial muscles are the most often implicated and lower limb involvement is less common. Winging of the scapulae are one characteristic finding which may necessitate surgical fixation. It is a progressive condition however prognosis is usually good with minor disability and lifespan unaffected.

Myotonic dystrophy is the most common muscular dystrophy of which symptoms include delayed relaxation of muscles wasting and weakness as well as cardiac conduction deficits, cataracts and characteristic facies. Becker muscular dystrophy usually presents in childhood with predominantly lower limb and girdle weakness. Patients with Emery-Dreifuss muscular dystrophy also usually present in childhood, characteristically with contractures and oculopharyngeal muscular dystrophy presents usually over the age of 40 with eyelid, facial and throat muscle weakness initially followed by pelvic and shoulder weakness.

### **Facioscapulohumeral muscular dystrophy**

Facioscapulohumeral muscular dystrophy (FSHMD) is an autosomal dominant form of muscular dystrophy. As the name suggests it typically affects the face, scapula and upper arms first. Symptoms typically presents by the age of 20 years

#### **Question 2 of 67**

A 67-year-old woman presents to her GP with progressive numbness and difficulty walking. Furthermore her daughter who was present mentions that she has been behaving strange over the past few months.

She is otherwise fit and well, apart from a ileal resection for treatment-resistant Crohn's disease 9 years ago.

Laboratory tests showed a low haematocrit and mean corpuscular volume of 110 fL. Blood smear analysis noted macrocytic red blood cells with hypersegmented neutrophils.

Which of the following is the most likely cause of the patient's presentation?



[Ferrochelatase deficiency4%](#) [Folate deficiency18%](#) [Intrinsic factor deficiency19%](#) [Iron deficiency anaemia5%](#) [Cobalamin deficiency54%](#)

The ileal resection suggests that the patient is not absorbing the vitamin B12-intrinsic factor complex, leading to vitamin B12 deficiency (aka. cobalamin deficiency), and subsequently subacute combined degeneration. This is further supported by the macrocytic anaemia with hypersegmented neutrophils. Folate deficiency causes the same blood film picture but does not present with neurological symptoms.

## **Subacute combined degeneration of spinal cord**

### Basics

- due to vitamin B12 deficiency
- dorsal + lateral columns affected
- joint position and vibration sense lost first then distal paraesthesia
- upper motor neuron signs typically develop in the legs, classically extensor plantars, brisk knee reflexes, absent ankle jerks
- if untreated stiffness and weakness persist

### Question 1 of 62

A 35-year-old female presents to the Emergency Department with three days of increasing weakness in the left arm and reduced visual acuity in the left eye. She was diagnosed with relapsing-remitting multiple sclerosis two years earlier. She takes fingolimod as maintenance therapy and denies any compliance issues.

On examination, she has weakness in wrist extension and finger abduction in the left hand and visual acuity in the left eye was measured at 6/24 with an associated reduction in colour saturation. Her blood tests were unremarkable and in particular, her white cell count was normal. Her MRI scan does show two new enhancing lesions in the right pericallosal region.

How should this be managed acutely?

[Commence high dose oral prednisone and wean over a month12%](#) [Commence intravenous dexamethasone7%](#) [Commence natalizumab infusion7%](#) [Commence high dose methylprednisolone for 3-5 days69%](#) [Biopsy the enhancing lesions4%](#)

Given that this patient has relapsed on maintenance therapy, and that she has multi-focal signs affecting vision and motor function, she should be admitted to hospital and commenced on high-dose intravenous methylprednisolone.

Acute relapses can be treated with either high dose oral prednisolone or intravenous therapy. The choice depends on multiple factors including the severity of symptoms, the requirement for hospital admission for monitoring, and co-morbidities such as diabetes and depression.

After this patient has recovered from this acute relapse a review of her maintenance therapy should occur, and this may be escalated through her neurologist based on a number of criteria.

## **Multiple sclerosis: management**

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

### **Acute relapse**

High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

### **Disease modifying drugs**

Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'
- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

## Some specific problems

### Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

### Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evaluation

### Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying
  - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

### Oscillopsia (visual fields appear to oscillate)

- gabapentin is first-line

## Question 2 of 62

A 77-year-old female was brought into hospital after waking with left arm weakness predominantly affecting the hand with a left sided facial droop in an upper motor neuron pattern. Her blood pressure on admission was 175/90 mmHg and her heart rate was 80 beats per minute and in sinus rhythm. Her blood glucose level on admission was 7.2 mmol/L.

Her initial CT brain showed some mild bi-temporal atrophic change and some chronic small vessel ischaemia without any acute ischaemic changes and in particular, no haemorrhage.

She was admitted with a suspected diagnosis of minor ischaemic stroke. Which of the following imaging modalities will confirm the diagnosis?

[CT cerebral angiogram \(CTA\)9%](#)[Fluid attenuated inversion recovery \(FLAIR\) MRI14%](#)[Thin slice non-contrast enhanced CT brain scan6%](#)[Diffusion weighted imaging \(DWI\) MRI64%](#)[Formal cerebral digital subtraction angiogram \(DSA\)7%](#)

DWI-MRI is the most sensitive and specific imaging modality for diagnosing acute stroke.

FLAIR MRI is sensitive for chronic ischaemic changes.

Both CTA and DSA may identify significant intravascular stenoses or thrombosis but are insensitive for small areas of acute ischaemic change.

Thin slice CT scans may identify established ischaemia with more sensitivity than a standard CT scan but is still inferior to DWI MRI.

In general, the purpose of the initial CT scan in accident and emergency for suspected ischaemic stroke patients is to exclude a haemorrhage.

## **Stroke: assessment**

Whilst the diagnosis of stroke may sometimes be obvious in many cases the presenting symptoms may be vague and accurate assessment difficult.

The FAST screening tool (Face/Arms/Speech/Time) is widely known by the general public following a publicity campaign. It has a positive predictive value of 78%.

A variant of FAST called the ROSIER score is useful for medical professionals. It is validated tool recommended by the Royal College of Physicians.

## **ROSIER score**

Exclude hypoglycaemia first, then assess the following:

<b>Assessment</b>	<b>Scoring</b>
Loss of consciousness or syncope	- 1 point
Seizure activity	- 1 point
New, acute onset of:	
• asymmetric facial weakness	+ 1 point

Assessment	Scoring
• asymmetric arm weakness	+ 1 point
• asymmetric leg weakness	+ 1 point
• speech disturbance	+ 1 point
• visual field defect	+ 1 point

A stroke is likely if > 0

### Question 3 of 62

A 50-year-old Caucasian female on holiday from Australia presents to the walk-in urgent care centre with four-day history of left-sided temporal headache, which is persistent and of gradual onset. In addition, she complains of double vision as well. She is known to have migraines but is relatively well-controlled. She is normally independent with no significant family history. She takes no regular medications except the oral contraceptive pill. On examination, you note a left sided loss of the afferent papillary reflex. She also has a loss of vertical gaze and is unable to adduct her left eye. She has a reduced sensation to light touch on the left forehead and cheek, not crossing the midline. What is the most likely diagnosis?

[Left space-occupying lesions](#)8% [Multiple sclerosis](#)9% [Right MCA territory ischaemic infarct](#)8% [Cavernous sinus thrombosis](#)68% [Migraine with aura](#)8%

The patient describes a clear history of loss of her 3rd cranial nerve, with the possible involvement of the left 4th, with V1 and V2 branches of the left trigeminal nerve. The only structure involving all these cranial nerves (and classically with the sympathetic postganglionic neuron) is the cavernous sinus. The patient has a number of risk factors for venous thrombotic disease, including recent long-haul flight and the oral contraceptive pill. The most likely causes are dehydration and VTE disease risk factors, but a carotid artery aneurysm should also be considered.

## Intracranial venous thrombosis

### Overview

- can cause cerebral infarction, much less common than arterial causes

- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

#### Features

- headache (may be sudden onset)
- nausea & vomiting

#### Sagittal sinus thrombosis

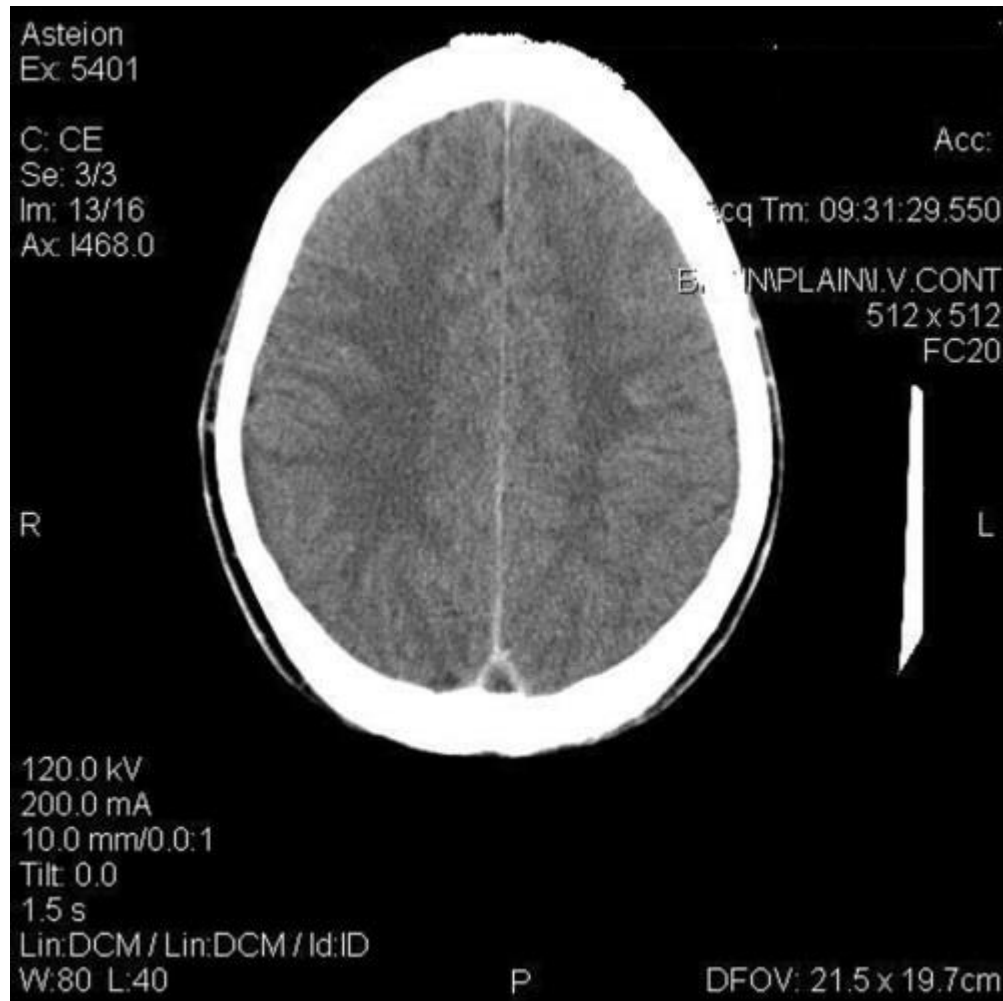
- may present with seizures and hemiplegia
- parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

#### Cavernous sinus thrombosis

- other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

#### Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



CT with contrast demonstrating a **superior sagittal sinus thrombosis** showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

#### Question 4 of 62

A 55-year-old cachectic male is brought into hospital after having been found on the floor by his sister, who visits him once a week. She reports a long history of depression and his appetite to have been poor for a number of years. He denies any loss of consciousness episodes, palpitations, chest pain, dysphagia or presyncopal symptoms. When asked how he ended up on

the floor, he vaguely reports to have slowly fallen from being generally weak and denies head injury. He does report a recent sore throat and dry cough. He is alert and orientated. On examination, he scores 3 and 4 out of 5 power in all movements. Lower limb reflexes could not be elicited with a tendon hammer but bilateral upgoing plantars are noted. Which treatment might reverse the underlying condition most rapidly?

[IV methylprednisolone 8% IV immunoglobulin infusion 24% Plasmapheresis 13% IV thrombolysis 5% IM vitamin B12 + IV pabrinex 50%](#)

The patient presents with upgoing plantars and absent ankle jerks. This should alert all MRCP candidates to 5 classic diagnoses: subacute combined degeneration of the cord (SCDC), motor neurone disease, Friedrich's ataxia, tabes dorsalis (syphilis) and dual peripheral with central pathology. In the context of cachexia and poor oral intake should alert a vitamin B12 deficiency, leading to a combination of peripheral and dorsal column degeneration, known as subacute combined degeneration of the cord. Vitamin B12 can in some cases reverse the neurology very rapidly.

## **Subacute combined degeneration of spinal cord**

### **Basics**

- due to vitamin B12 deficiency
- dorsal + lateral columns affected
- joint position and vibration sense lost first then distal paraesthesia
- upper motor neuron signs typically develop in the legs, classically extensor plantars, brisk knee reflexes, absent ankle jerks
- if untreated stiffness and weakness persist

### **Question 1 of 57**

A 24-year-old female is reporting difficulty in walking in an inpatient rehabilitation unit during recovery from spinal surgery. Six weeks previously, she underwent emergency spinal haematoma evacuation surgery under the neurosurgeons from T2 to T4 after sustaining a fall playing netball. She was previously fit and well, with no past medical history, giving birth to a healthy baby boy 18 months ago.

On examination, the patient has normal tone in her upper and lower limbs. Examination of her power while lying on her bed demonstrates 5/5 on the MRC power scale with normal sensation



to cotton wool, pin prick and proprioception. Reflexes were present (2+) in her biceps, triceps, supinator, patella and ankles, both plantars were downgoing. On walking, the patient's gait is markedly abnormal, with both feet sliding along the floor for 80 metres of walking without lifting of her feet between steps. Cognition is intact. What is the optimal management?

[Repeat MRI head8%Repeat MRI whole spine19%Nerve conduction studies and electromyography21%Lumbar puncture5%Education and reassurance47%](#)

This patient's gait is inconsistent with any pattern of organic pathology: it is inconsistent to be unable to lift your feet but have normal ankle dorsiflexion and plantarflexion. The patient has a combination of recent significant organic pathology and inorganic pathology, which is frequently the case in functional neurological disorders. Repeat MRI imaging, electrophysiology or lumbar puncture are unlikely to help and only medicalise the disorder. It is crucial to reinforce this message by avoiding unnecessary investigations or treatments. Management of functional neurology is based on education and reassurance, telling the patient that it is a 'conceptualisation' problem and not an issue with the brain or nerves. Psychiatric input may also have a role in this situation if the patient continues to be refractory to first line management: cognitive behavioural therapy may be helpful.

## **Unexplained symptoms**

There are a wide variety of psychiatric terms for patients who have symptoms for which no organic cause can be found:

### Somatisation disorder

- multiple physical SYMPTOMS present for at least 2 years
- patient refuses to accept reassurance or negative test results

### Hypochondrial disorder

- persistent belief in the presence of an underlying serious DISEASE, e.g. cancer
- patient again refuses to accept reassurance or negative test results

### Conversion disorder

- typically involves loss of motor or sensory function
- the patient doesn't consciously feign the symptoms (factitious disorder) or seek material gain (malingering)

- patients may be indifferent to their apparent disorder - la belle indifference - although this has not been backed up by some studies

### Dissociative disorder

- dissociation is a process of 'separating off' certain memories from normal consciousness
- in contrast to conversion disorder involves psychiatric symptoms e.g. Amnesia, fugue, stupor
- dissociative identity disorder (DID) is the new term for multiple personality disorder as is the most severe form of dissociative disorder

### Munchausen's syndrome

- also known as factitious disorder
- the intentional production of physical or psychological symptoms

### Malingering

- fraudulent simulation or exaggeration of symptoms with the intention of financial or other gain

### Question 2 of 57

A 16-year-old boy is brought into the emergency department by his mother after an episode of unresponsiveness while walking, lasting transiently for seconds before fully resolving. He has no recollection of these episodes. He was diagnosed with absence seizures aged 11 and was previously prescribed anti-epileptics. These had been gradually weaned off two years ago by his neurologists following a 3-year seizure-free period.

Over the past 48 hours, he has now had 4 of his typical absences. You decide to prescribe an anti-epileptic. Which antiepileptic should be avoided?

[Carbamazepine40%](#) [Sodium valproate27%](#) [Lamotrigine11%](#) [Levetiracetam10%](#) [No contraindications12%](#)

Classically, carbamazepine can aggravate juvenile myoclonic epilepsy and absence seizures<sup>1</sup>. In general, carbamazepine should always be avoided in patients where the type of seizure is uncertain. It is otherwise a useful AED in the treatment of partial or secondary generalised

seizures.

1. WD Shields, Saslow E. Myoclonic, atonic, absence seizures following institution of carbamazepine therapy in children. Neurology 1983; 33:1487

## **Absence seizures**

Absence seizures (petit mal) are a form of generalised epilepsy that is mostly seen in children. The typical age of onset of 3-10 years old and girls are affected twice as commonly as boys

### Features

- absences last a few seconds and are associated with a quick recovery
- seizures may be provoked by hyperventilation or stress
- the child is usually unaware of the seizure
- they may occur many times a day
- EEG: bilateral, symmetrical 3Hz spike and wave pattern

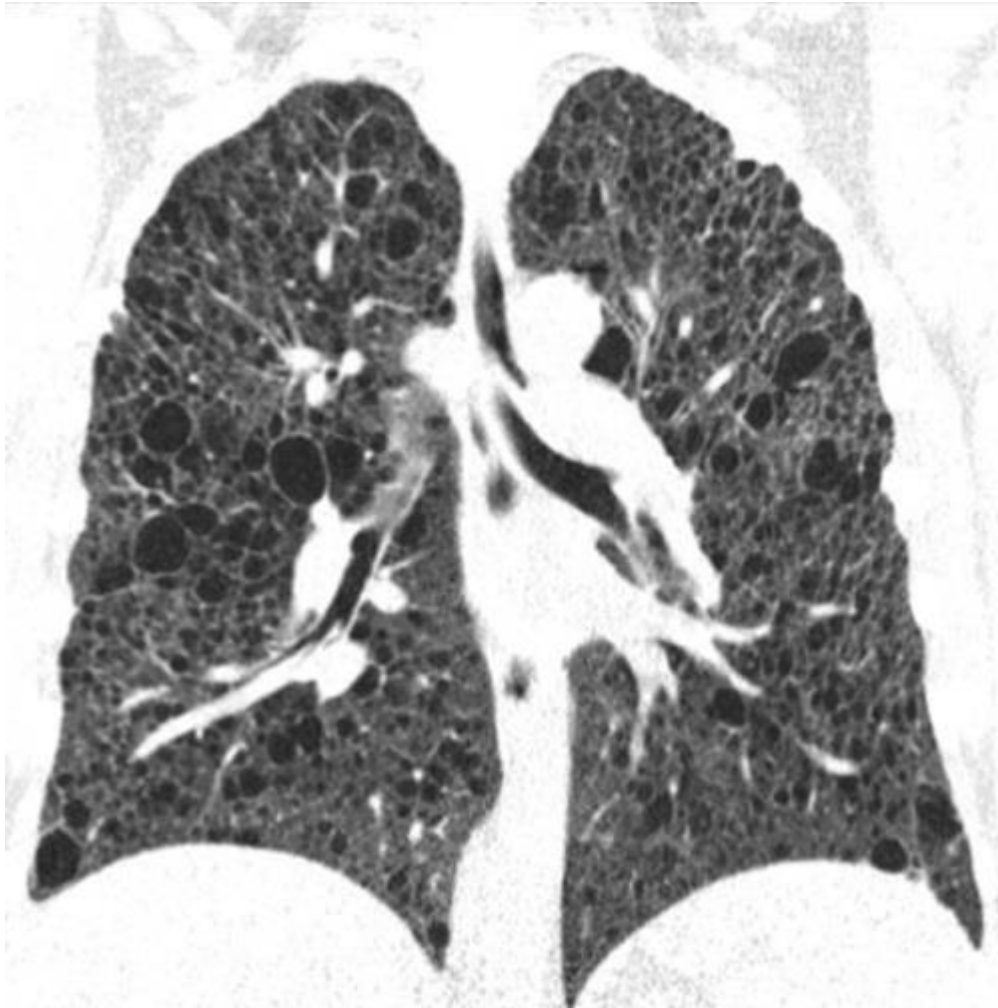
### Management

- sodium valproate and ethosuximide are first-line treatment
- good prognosis - 90-95% become seizure free in adolescence

### Question 3 of 57

A 39-year-old woman with known tuberous sclerosis is referred to the respiratory clinic after developing progressive dyspnoea. Her GP had requested a chest x-ray which showed significant changes.

The CT scan is shown below:



© Image used on license from [Radiopaedia](#)



What complication has developed?

[Metastatic angiomyolipoma](#)8%[Lymphangioleiomyomatosis](#)59%[Lung rhabdomyomas](#)6%[Lung angiofibromas](#)22%[Subependymal giant cell astrocytoma](#)5%

The CT demonstrate innumerable small regular lung cysts diffusely distributed throughout the lungs, the typical appearance of lymphangioleiomyomatosis (LAM). This disorder may occur alone or in association with tuberous sclerosis.

## Tuberous sclerosis

Tuberous sclerosis (TS) is a genetic condition of autosomal dominant inheritance. Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

### Cutaneous features

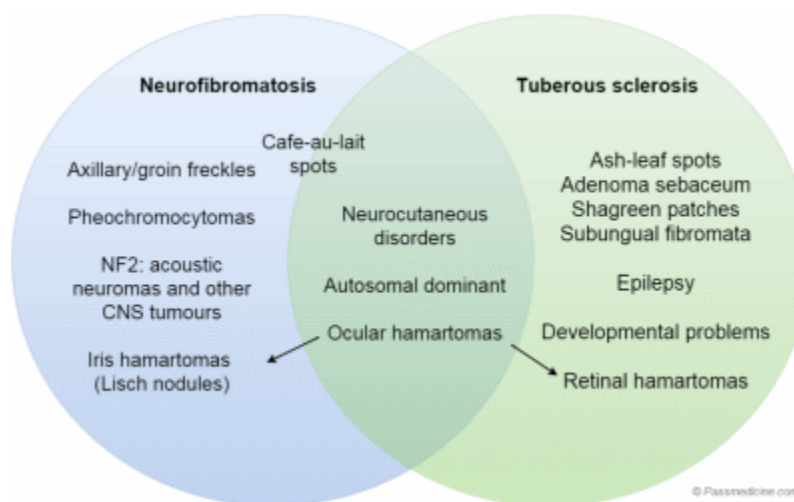
- depigmented 'ash-leaf' spots which fluoresce under UV light
- roughened patches of skin over lumbar spine (Shagreen patches)
- adenoma sebaceum (angiofibromas): butterfly distribution over nose
- fibromata beneath nails (subungual fibromata)
- café-au-lait spots\* may be seen

### Neurological features

- developmental delay
- epilepsy (infantile spasms or partial)
- intellectual impairment

### Also

- retinal hamartomas: dense white areas on retina (phakomata)
- rhabdomyomas of the heart
- gliomatous changes can occur in the brain lesions
- polycystic kidneys, renal angiomyolipomata
- lymphangiomyomatosis: multiple lung cysts





Comparison of neurofibromatosis and tuberous sclerosis. Note that whilst they are both autosomal dominant neurocutaneous disorders there is little overlap otherwise

\*these of course are more commonly associated with neurofibromatosis. However a 1998 study of 106 children with TS found café-au-lait spots in 28% of patients

#### Question 1 of 52

A 32-year-old man had a compressive pituitary macroadenoma surgically removed in France 4 weeks ago and has been on pituitary hormone replacement since, including growth hormone. Surgery was uncomplicated and he initially made a good recovery. He has no other past medical history. He has now developed, over the last 1-2 weeks, poor balance, with a broad-based gait. He has also become extremely forgetful. On examination, he has an ataxic gait and you also observe occasional myoclonic limb movements. His MMSE score is 22/30. Clinical examination is otherwise unremarkable, as are routine blood investigations. Given the likely diagnosis, what might you expect to find on his MRI brain?

[Areas of demyelination in the cerebellum 20%](#)[An area of high T2 signal in the right middle cerebral artery territory with restricted diffusion on diffusion-weighted sequences 14%](#)[High T2 signal in the posterior thalamus 35%](#)[Leptomeningeal enhancement 19%](#)[Loss of grey-white matter differentiation 12%](#)

The diagnosis is Creutzfeldt-Jakob disease (CJD) from an iatrogenic source.

The use of prion-contaminated medication, grafts and instruments may result in iatrogenic CJD. The current worldwide total of growth-hormone-associated cases of CJD is 226. Most cases occurred in France (119 cases/1,880 recipients; attack rate 6.3%), the United Kingdom (65 cases/1,800 recipients; attack rate 3.6%), and the United States (29 cases/7,700 recipients; attack rate 0.4%). No new case has been identified since 2008 but would be important to recognise this condition and how it presents if it did, as it is invariably fatal -so patients need to be made aware of their prognosis.

The clinical features of the disease vary according to the route of inoculation.

Central inoculation, eg from infected neurosurgical instruments, results in a rapidly progressive neurodegenerative disease similar to sporadic CJD, characterised by ataxia, dementia, myoclonus, rigidity, and akinetic mutism. Survival is 2-12 months.

Peripheral inoculation, eg from the use of the old human growth hormone products, results in a slightly less acute disease -characterised by progressive cerebellar ataxia and dementia. Survival is 8-18 months.

## **Creutzfeldt-Jakob disease**

Creutzfeldt-Jakob disease (CJD) is rapidly progressive neurological condition caused by prion proteins. These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.

### Features

- dementia (rapid onset)
- myoclonus

### Investigation

- CSF is usually normal
- EEG: biphasic, high amplitude sharp waves (only in sporadic CJD)
- MRI: hyperintense signals in the basal ganglia and thalamus

### Sporadic CJD

- accounts for 85% of cases
- 10-15% of cases are familial
- mean age of onset is 65 years

### New variant CJD

- younger patients (average age of onset = 25 years)
- psychological symptoms such as anxiety, withdrawal and dysphonia are the most common presenting features
- the 'prion protein' is encoded on chromosome 20 - it's role is not yet understood
- methionine homozygosity at codon 129 of the prion protein is a risk factor for developing CJD - all patients who have so far died have had this
- median survival = 13 months

## Other prion diseases

- kuru
- fatal familial insomnia
- Gerstmann Straussler-Scheinker disease

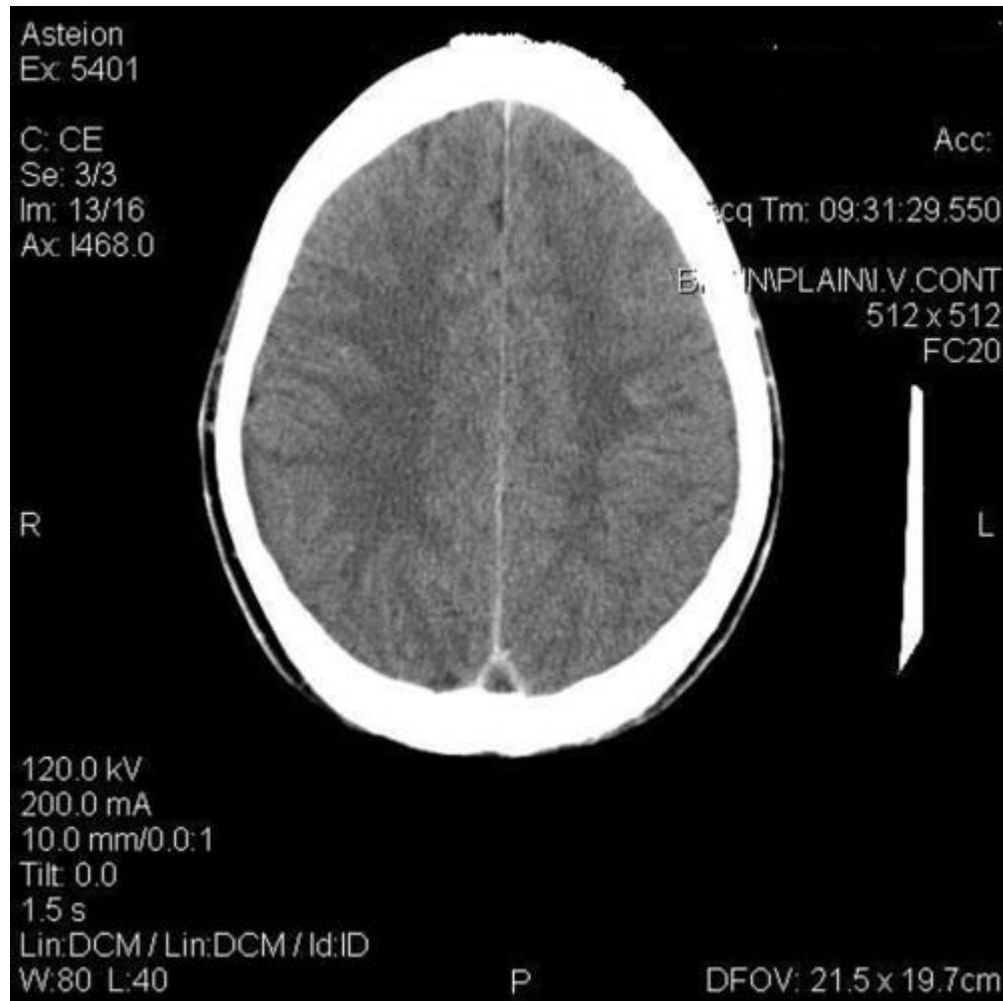
## Question 2 of 52

A 19-year-old female is admitted to the Emergency Department after suffering a seizure. Her friends report that she is normally fit and well but had been complaining of a bad headache for the past few hours.

On examination her GCS is 13/15 (M6 V4 E3). No focal neurological deficit is noted. She appears slightly confused and is holding her head in her hands. Her pulse rate is 90/min with a temperature of 37.2°. No neck stiffness is noted.

A CT scan with contrast is requested:





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What is the most likely diagnosis?

[Extradural haemorrhage](#)4% [Superior sagittal sinus thrombosis](#)68% [Herpes simplex encephalitis](#)8% [Subarachnoid haemorrhage](#)15% [Meningioma](#)5%

The CT with contrast demonstrates a superior sagittal sinus thrombosis showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis.

## **Intracranial venous thrombosis**

### Overview

- can cause cerebral infarction, much less common than arterial causes
- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

### Features

- headache (may be sudden onset)
- nausea & vomiting

### Sagittal sinus thrombosis

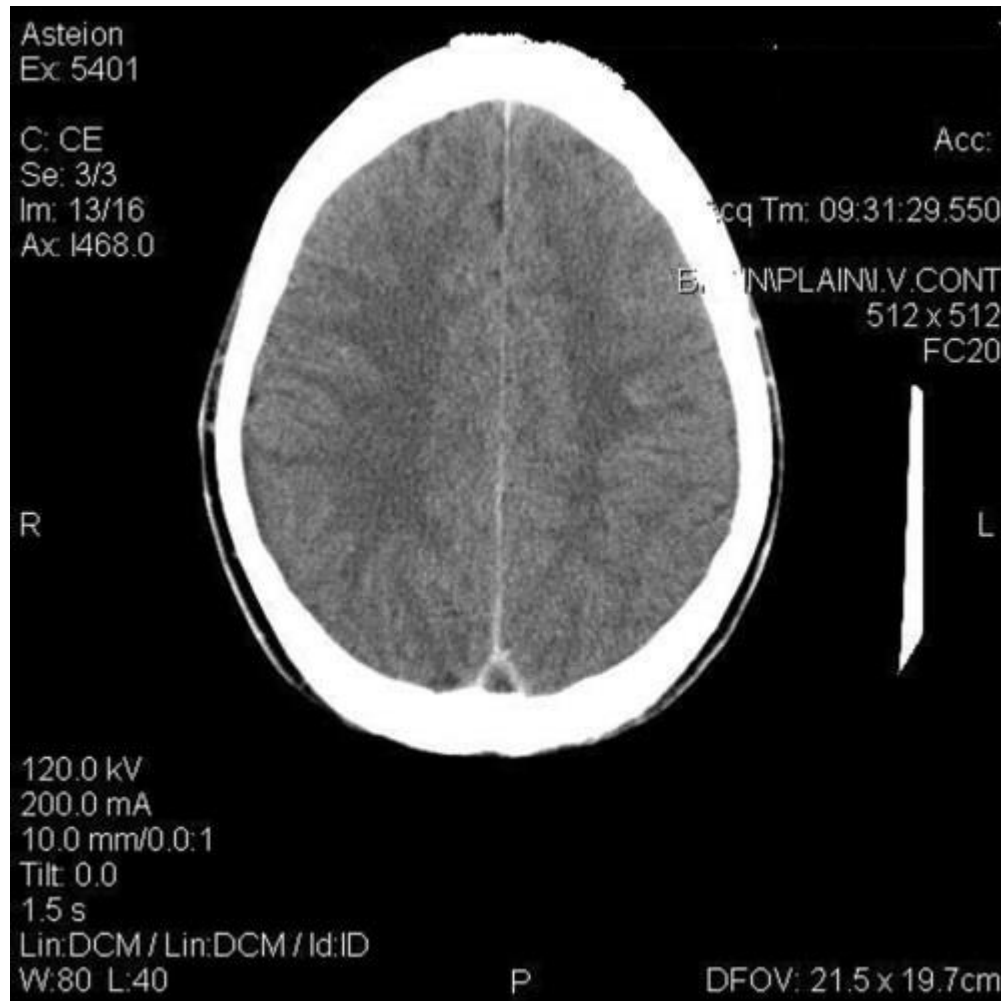
- may present with seizures and hemiplegia
- parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

### Cavernous sinus thrombosis

- other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

### Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies



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CT with contrast demonstrating a **superior sagittal sinus thrombosis** showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

#### Question 4 of 52

A 43-year-old right-handed female legal secretary has presented into your general medical clinic in an extremely distressed state. Over the past 2 weeks, she has been 'unable to write'. When questioned further, she reports that she 'wants to write but my hand just stops as soon as I pick up the pen.' She has no past medical history, lives with her husband and is a non-smoker and non-

drinker. On examination, her neurological examination is unremarkable. You ask her to write. Her hand and fingers suddenly flex, resulting in illegible handwriting. What is the most likely diagnosis?

[Psychogenic functional neurology37%](#)[Focal dystonia41%](#)[Dominant parietal lobe space occupying lesion9%](#)[Right median nerve palsy6%](#)[Brachial plexopathy6%](#)

The patient describes a history suggestive of writers cramp, a focal dystonia characterised by flexion, extension or rotation of the muscles of the hand. The underlying pathophysiology is unclear but is thought to relate to a change in the plasticity of cortical networks.

## **Focal dystonia**

Focal dystonias are distinguished from segmental or generalised dystonias, which involve a greater number of muscle groups. Focal dystonias are often relieved by a geste antagoniste, in which palpation of another unaffected part of the body leads to relief of symptoms, thought to be a result of alternative sensory input to cortical networks with altered plasticity.

### **Question 10 of 52**

You are called to see a 67 year old lady by the Psychiatry SHO who is asking for your opinion on management. Over the past 3 weeks, her husband has become increasingly concerned by her behaviour. She has become suspicious of him and accused him of stealing my true husband. Initially the lady would avoid her husband and refuse to eat food that she had prepared but today she threatened him with a knife and the police had to be called.

The psychiatry SHO is concerned as he notes that she was admitted to hospital 5 weeks ago and was treated for a suspected urinary tract infection with intravenous antibiotics. Subsequent testing showed the pathogen to be an extended spectrum beta lactamase producing bacteria. She currently has a temperature of 38.7 degrees heart rate 105bpm regular RR 18 Sats 99% on room air. Her husband notes that she has been spending more time in the toilet over the past 3 weeks but is unsure if this is due to her paranoia. Blood tests have not been acquired at this point due to no co-operation of the patient.

Her husband describes an episode 30 years ago where she required antidepressants, antipsychotics and ECT after a close family bereavement. She also takes amlodipine 5mg PO OD for hypertension. She is otherwise well and has no history of cognitive problems. Her husband states that there is a strong history of mental health problems in her family but he is unable to be more specific.

When you speak to her she appears to be confused and scores 19/30 on the Mini Mental State Examination. She can point to, name and recognise her husband and can also pick him out from pictures. However, she tells you that the man standing next to her is not her husband but a lookalike who has replaced him. Despite all your best efforts to show evidence to the contrary she cannot be persuaded to change her opinion.

Which of the following below would best describe her presentation:

[Delirium causing Cotard syndrome13%](#)[Delirium causing Fregoli syndrome16%](#)[Delirium causing Capgras syndrome55%](#)[Late onset schizophrenia causing Capgras syndrome10%](#)[Atypical severe depression6%](#)

Firstly, this woman has features that suggest delirium having a factor to play in her presentation: fever, acute cognitive impairment, infective symptoms, recent treatment for a highly resistant infection. Late onset schizophrenia is very rare and when it does occur has no association with family history of mental health problems or personal history of depression. In addition the duration of symptoms is probably too rapid for a late onset schizophrenia.

Secondly, the woman is describing a delusion where she believes her husband to be replaced by an imposter. This is known as Capgras syndrome and can be seen in organic states such as delirium as well as in schizophrenia. It is rare but is most commonly seen in older women. The delusion most commonly relates to a life partner and can sometimes lead to serious violence being perpetrated against the supposed imposter.

Cotard syndrome is a nihilistic delusion seen in severely depressed people where they believe that they, or a part of their body is dead.

In Fregoli syndrome, the patient believes that an individual (who is almost always a persecutory figure and someone close to them) has taken on many different guises. This syndrome is named after an artist called Leopoldo Fregoli renowned for his ability to change costumes very quickly. A person with Fregoli syndrome will identify several different strangers as being the persecutor in disguise.

## **Capgras syndrome**

Capgras syndrome refers to a disorder in which a person holds a delusion that a friend or partner has been replaced by an identical-looking impostor.

## Question 1 of 42

A 63-year-old woman returns to neurology clinic for review with her husband. She was diagnosed with Parkinson's disease two years ago and was started on ropinirole six months ago as her symptoms were becoming difficult to manage. She was mainly concerned with the rigidity of her movements. Since then she has improved remarkably, and her movements are much better, with reduced rigidity on examination. Her mood has also been improving with the relief from her symptoms.

However, her husband has become concerned that she has been increasingly spending large amounts on shopping, something which has not done before and that he feels is out of character. What is the most likely explanation?

[Normal behaviour](#)5% [Progression of Parkinson's disease](#)5% [Lewy-body dementia](#)9% [Dopaminergic dysregulation syndrome](#)37% [Impulse control disorder](#)43%

The correct answer is impulse control disorder. This is a patient recently started on a dopamine agonist who has subsequently developed reduced impulse control. This is not an unimportant symptom and can have significant implications, especially for someone with a history of gambling. Before starting a dopamine antagonist this risk has to be explained to the patient. This symptom does not fit any of the other diagnoses described: there is no cognitive decline as would be expected with dementia, no worsening of Parkinsonian symptoms and no mood changes as would be expected in dopaminergic dysregulation syndrome.

Source:

Tarsay, Daniel. 'Pharmacologic Treatment of Parkinson Disease.' Ed. Howard I. Hurtig. UpToDate. N.p., 13 Sept. 2016.

## Parkinson's disease: management

NICE published guidelines in 2017 regarding the management of Parkinson's disease.

For first-line treatment:

- if the motor symptoms are affecting the patient's quality of life: levodopa
- if the motor symptoms are not affecting the patient's quality of life: dopamine agonist (non-ergot derived), levodopa or monoamine oxidase B (MAO-B) inhibitor

Whilst all drugs used to treat Parkinson's can cause a wide variety of side-effects NICE produced tables to help with decision making:

	<b>Levodopa</b>	<b>Dopamine agonists</b>	<b>MAO-B inhibitors</b>
<b>Motor symptoms</b>	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
<b>Activities of daily living</b>	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
<b>Motor complications</b>	More motor complications	Fewer motor complications	Fewer motor complications
<b>Adverse events</b>	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

\* excessive sleepiness, hallucinations and impulse control disorders

If a patient continues to have symptoms despite optimal levodopa treatment or has developed dyskinesia then NICE recommend the addition of a dopamine agonist, MAO-B inhibitor or catechol-O-methyl transferase (COMT) inhibitor as an adjunct. Again, NICE summarise the main points in terms of decision making:

	<b>Dopamine agonists</b>	<b>MAO-B inhibitors</b>	<b>COMT inhibitors</b>	<b>Amantadine</b>
<b>Motor symptoms</b>	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
<b>Activities of daily living</b>	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
<b>Off time</b>	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
<b>Adverse events</b>	Intermediate risk of adverse events	Fewer adverse events	More adverse events	No studies reporting this outcome
<b>Hallucinations</b>	More risk of	Lower risk of	Lower risk of	No studies reporting

Dopamine agonists	MAO-B inhibitors	COMT inhibitors	Amantadine
hallucinations	hallucinations	hallucinations	this outcome

### Specific points regarding Parkinson's medication

NICE reminds us of the risk of acute akinesia or neuroleptic malignant syndrome if medication is not taken/absorbed (for example due to gastroenteritis) and advise against giving patients a 'drug holiday' for the same reason.

Impulse control disorders have become a significant issue in recent years. These can occur with any dopaminergic therapy but are more common with:

- dopamine agonist therapy
- a history of previous impulsive behaviours
- a history of alcohol consumption and/or smoking

If excessive daytime sleepiness develops then patients should not drive. Medication should be adjusted to control symptoms. Modafinil can be considered if alternative strategies fail.

If orthostatic hypotension develops then a medication review looking at potential causes should be done. If symptoms persist then midodrine (acts on peripheral alpha-adrenergic receptors to increase arterial resistance) can be considered.

### Further information regarding specific anti-Parkinson's medication

#### Levodopa

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- unwanted effects: dyskinesia (involuntary writhing movements), 'on-off' effect, dry mouth, anorexia, palpitations, postural hypotension, psychosis, drowsiness
- no use in neuroleptic induced parkinsonism

#### Dopamine receptor agonists

- e.g. Bromocriptine, ropinirole, cabergoline, apomorphine



- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
- patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence
- more likely than levodopa to cause hallucinations in older patients. Nasal congestion and postural hypotension are also seen in some patients

#### MAO-B (Monoamine Oxidase-B) inhibitors

- e.g. Selegiline
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

#### Amantadine

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
- side-effects include ataxia, slurred speech, confusion, dizziness and livedo reticularis

#### COMT (Catechol-O-Methyl Transferase) inhibitors

- e.g. Entacapone, tolcapone
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
- used in conjunction with levodopa in patients with established PD

#### Antimuscarinics

- block cholinergic receptors
- now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g. procyclidine, benzotropine, trihexyphenidyl (benzhexol)

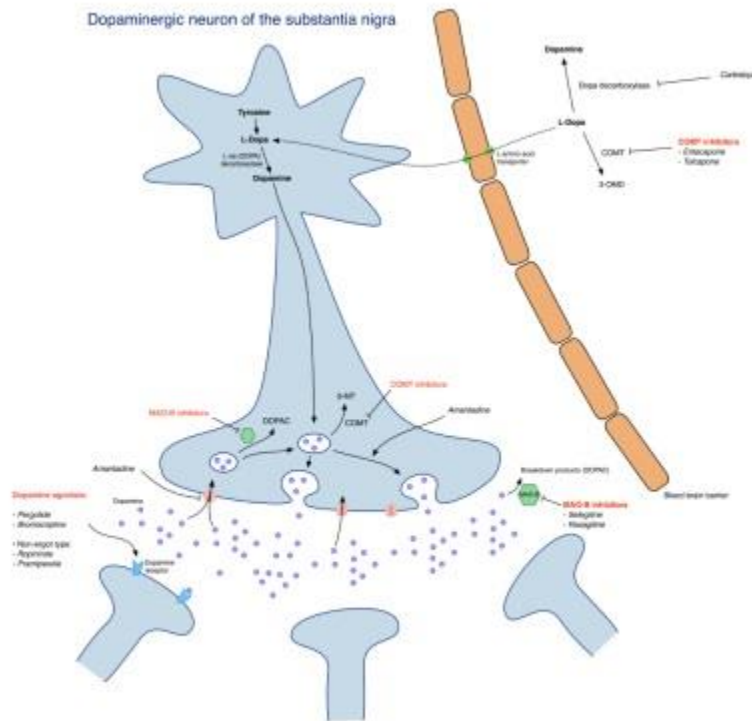


Image sourced from [Wikipedia](https://en.wikipedia.org/wiki/File:Dopamine_synthesis_and_action.png)



Diagram showing the mechanism of action of Parkinson's drugs

#### Question 6 of 42

An 18-year-old female is admitted to hospital with worsening lower limb weakness. She states that it started in her ankles, but now she is unable to stand from a squatting position which is abnormal for her. On examination, she has reduced power in ankle plantar and dorsiflexion bilaterally as well as some mild weakness in her hip extensors. Her hand grip strength is normal.

A cerebrospinal fluid (CSF) study is carried out and based on the clinical syndrome and the result she is diagnosed with Guillain-Barre Syndrome (GBS).

Which of the following treatments should be commenced in the acute setting?

[Intravenous methylprednisolone12%](#) [Intravenous immunoglobulin74%](#) [Oral prednisone5%](#) [Rituximab4%](#) [Pyridostigmine4%](#)

Immunomodulatory treatment has been proven to hasten recovery in GBS. Intravenous

immunoglobulin (IVIG) and plasma exchange have proved equally effective, however, IVIG is often the initial treatment for practical reasons.

Corticosteroids (oral and intravenous) have not been found to have a clinical benefit in GBS. Consequently, this class of drugs is not currently employed in the treatment of the syndrome.

## **Guillain-Barre syndrome: management**

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*).

### Management

- plasma exchange
- IV immunoglobulins (IVIG): as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function

### Prognosis

- 20% suffer permanent disability, 5% die

Question 1 of 32

A 17-year-old Caucasian male with no past medical history presents with his first episode of sudden onset left leg weakness and numbness on his anterior left thigh, of sudden onset and persistent after 4 days. On examination, you note 3/5 weakness on flexion of his left hip and loss of sensation to light touch, pain and temperature on his anterior left thigh in the sensory nerve root L1 distribution. A contrasted MRI scan of the patient's spine reveals a hyperintense T2 signal partially within the left side of the cord at the L1, with corresponding enhancement with gadolinium. No masses were observed. Further imaging of the brain is awaited. What is the most likely diagnosis at present?

[Multiple sclerosis26%](#)[Left spinal cord tumour9%](#)[Left anterior spinal ischaemic stroke14%](#)[Left transverse myelitis46%](#)[Guillain Barre syndrome5%](#)

The history, examination and radiological evidence are strongly suggestive of partial L1 transverse myelitis. The key question is whether this represents a diagnosis of multiple sclerosis (MS) or not. The diagnosis of MS is determined by the McDonald criteria, first proposed in 2001 and most recently revised in 2010<sup>1</sup>. The lesions or clinical episodes suggestive of acute demyelinating episodes must be disseminated in both time and place. As a result, a patient presenting with only one symptomatic episode can be diagnosed with MS if their MRI scans demonstrate demyelinating plaques that are:

- i) distinguished in age from the current symptomatic lesion
- ii) In at least two of 4 areas typical of MS (periventricular, juxtacortical, infratentorial, spinal cord white matter).

In this case, only one episode in time and space has been demonstrated so far. Although a risk of future MS diagnosis is acknowledged and may go on to be proven following MRI of the head, the diagnosis remains transverse myelitis at present.

It is often quoted that in patients diagnosed with transverse myelitis after their first symptomatic episode, only a small proportion go on to be diagnosed with MS later in their lives. However, more recent evidence suggests the pattern of transverse myelitis is important: only 5-10% of patients with complete transverse myelitis will be diagnosed with MS, with a viral febrile illness the most likely underlying cause. Patients with incomplete transverse myelitis have up to 72% risk of MS-consistent plaques found on MRI head, with 60-90% subsequently being diagnosed MS within 5 years<sup>2</sup>.

Old MS plaques appear better defined on T1 and T2 imaging than acute lesions. Contrast studies with gadolinium are also helpful: acute plaques tend to enhance to a greater degree on T1 imaging, correlated to acute inflammation that persists for up to 8 weeks and diminishes on treatment with glucocorticoids.

1. Montalban X, Tintoré M, Swanton et al. MRI criteria for MS in patients with clinically isolated syndromes. *Neurology*. 2010;74(5):427

2. Morrissey SP, Miller DH, Kendall BE et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. *Brain*. 1993;116 ( Pt 1):135

## **Transverse myelitis**

Causes of transverse myelitis

- viral infections: varicella zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, human immunodeficiency virus
- bacterial infections: syphilis, Lyme disease
- post-infectious (immune mediated)
- first symptom of multiple sclerosis (MS) or neuromyelitis optica (NMO)

#### Question 6 of 32

A 32-year-old female is seen in neurology clinic due to a 4-month history of headaches. She described having headaches most days on waking up, which were throbbing in nature. She found that they eased off after mobilising and that coughing made them worse. She reported a couple of episodes of blurred vision on waking, but no nausea or vomiting. Her general practitioner arranged for an outpatient magnetic resonance head scan which was normal. Her body mass index (BMI) had been 27 kg/m<sup>2</sup>, but on advice from her general practitioner she had lost weight, and her BMI was now 23 kg/m<sup>2</sup>. She was not on any regular medications, other than paracetamol and ibuprofen which she had been using regularly for her headaches.

There was no focal neurological deficit on examination, and her visual acuity was normal. On fundoscopy, there was a mild degree of papilloedema. Blood pressure was 125/82mmHg. Blood tests were unremarkable.

What is the most appropriate next step in management?

[Lumbar-peritoneal shunt](#)11% [Optic nerve fenestration](#)6% [Cessation of paracetamol and ibuprofen](#)22% [Acetazolamide](#)57% [Sumatriptan](#)4%

The postural nature of this patient's headaches, and the fact that they are exacerbated by coughing are suggestive of raised intracranial pressure. In a young woman with a normal magnetic resonance scan, this is suggestive of idiopathic intracranial hypertension.

In overweight patients, the initial management strategy is weight loss, which may be enough to relieve symptoms. This patient has already lost weight and has a normal body mass index, but her headaches persist, so additional measures are required. Cessation of any causative agents would also be important (e.g. tetracyclines, retinoids, lithium).

Acetazolamide is useful in controlling mild disease that is resistant to the conservative measures mentioned above. Repeated lumbar puncture may also be used to lower intracranial pressure. In acute disease, corticosteroids are sometimes beneficial. If there is significant visual loss despite medical therapy surgical interventions such as optic nerve sheath fenestration or lumbar-peritoneal shunt insertion may be necessary.

Analgesia-induced headache and migraine are important causes of recurrent headache, but would

not cause the postural association seen in this case, so cessation of analgesic agents and commencement of sumatriptan are not appropriate treatments.

## **Idiopathic intracranial hypertension**

Idiopathic intracranial hypertension (also known as pseudotumour cerebri and formerly benign intracranial hypertension) is a condition classically seen in young, overweight females.

### Features

- headache
- blurred vision
- papilloedema (usually present)
- enlarged blind spot
- sixth nerve palsy may be present

### Risk factors

- obesity
- female sex
- pregnancy
- drugs\*: oral contraceptive pill, steroids, tetracycline, vitamin A, lithium

### Management

- weight loss
- diuretics e.g. acetazolamide
- topiramate is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

\*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

### Question 8 of 32

A 58 year old man presents to Accident and Emergency with his wife complaining of memory loss. His first noticed a problem when he had difficulty making breakfast in the morning. When you question him, he has no memory of the events of today and patchy memory of the events of the past week although his wife informs you that he had no problem with his memory yesterday. He appears extremely anxious about his memory loss and repeatedly asks you 'Have I got dementia?'. He is able to remember his name and date of birth and recognise and name his wife. However, when using the toilet, he becomes lost and is unable to find his way back to the cubicle.

On examination his HS 1 + 2 + 0, he has corneal arcus, chest is clear. There is reduced power 4/5 to all arm movements in the right arm with normal reflexes, tone and sensation. His wife tells you that this has been present for several years following a stroke. There is no facial droop, there is no dysarthric speech or any other peripheral focal neurology and there are no cerebellar signs. Gait is normal.

He is able to count back from 20-1 and can name objects you present to him without difficulty. However he scores 0/3 on the delayed recall section of the MMSE. He is alert and fully responsive throughout the consultation.

Past medical history is of previous left sided middle cerebral territory infarct and one previous TIA one year ago. Hypercholesterolemia, hypertension. He has a 20 pack year history of smoking and used to drink 4-6 units of alcohol per day for 20 years but stopped this 25 years ago and his wife corroborates this information. His medications include Clopidogrel, Atorvastatin, Ramipril and Bendroflumethiazide.

CT Brain was performed 3 hours after waking up and is consistent with an old left sided infarct. No other abnormality detected.

What is the most appropriate treatment for this diagnosis?

[Intravenous thiamine and Vitamin B14% Oral thiamine and vitamin B10% Thrombolysis6% Donepezil19% Supportive care only50%](#)

The answer is E. This man has a diagnosis of transient global amnesia. TGA is characterised by a sudden onset of global loss of recent memory and impaired new learning with no other cognitive defects. These patients are often very aware of their memory loss making them extremely anxious. Because of the dense anterograde amnesia, it is also characterised by repetitive questioning. This is sometimes called the broken record syndrome Loss of personal identity effectively rules out TGA Patients are alert and responsive during the episode

TGA is probably due to a transient malfunctioning of the limbo-hippocampal system which is involved in the formation of new memories and retrieval of recent memories. It normally presents in the 5th decade of life in those with pre-existing vascular risk factors, meaning there is probably a cerebro-vascular component but the cause is not known. TGA resolves spontaneously

without need for treatment except for re-assurance and subsequent control of vascular risk factors.

Options A and B are inappropriate because the diagnosis is not Wernicke-Korsakoff syndrome. The presentation is too acute and too long after his heavy drinking of alcohol to be a likely diagnosis. Although there is similar defects in memory, there are normally defects in attention, concentration, frontal lobe functioning and is accompanied by symptoms such as apathy and withdrawal.

Option C is inappropriate as thrombolysis is not a treatment for TGA. In addition, thrombolysis would not usually be given to someone who has woken up with symptoms suggestive of a stroke, even if the time window is less than 4.5 hours.

Option D is inappropriate as the diagnosis is not dementia. The onset of symptoms are too acute for this diagnosis to be considered.

## **Transient global amnesia**

### Overview

- presents with transient loss of memory function
- patients may appear anxious and repeatedly ask the same question
- patients have no recall of events after the attack
- aetiology is unknown, thought to be due to transient ischaemia to the thalamus (in particular the amygdala and hippocampus)

### Question 10 of 32

A 27 year-old woman attends the neurology clinic complaining of headache and visual disturbance. She has recently immigrated from Ghana. Her symptoms began approximately one month ago, shortly after the birth of her first child. She experiences dull frontal headache which is worst in the mornings and on coughing or straining, as well as transient episodes of 'darkening' of her vision. She saw a doctor in Ghana and was diagnosed with idiopathic intracranial hypertension. She is taking acetazolamide 250mg BD and no other medication.

On examination the visual fields are markedly constricted and the right blind spot is enlarged.



Fundoscopy shows bilateral papilloedema worse on the right. The remainder of the neurological examination is unremarkable. BMI is 18 kg/m<sup>2</sup>.

Plain computed tomography of the brain is normal.

Incidentally as she is leaving the clinic she mentions that she has also been experiencing pins and needles in the hands and feet.

What is the best course of action?

[Increase dose of acetazolamide](#)5%[Request nerve conduction studies](#)8%[Organise for therapeutic lumbar puncture](#)17%[Refer to neurosurgeons for consideration of ventriculo-peritoneal shunting](#)22%[Request CT venography](#)48%

The history of headache suggestive of raised intracranial pressure associated with transient visual obscurations, as well as the examination findings, are all compatible with idiopathic intracranial hypertension (IIH). However, the onset of symptoms in the puerperium, in a slim patient with no other risk factors for IIH, raises the suspicion that this may actually be a cerebral venous sinus thrombosis. All patients with IIH should have imaging of the venous system with CT or MR to exclude a thrombus which can be more appropriately treated with anticoagulation.

Therapeutic lumbar puncture can ease the headache of IIH but is a short-term measure. Ventriculo-peritoneal shunting can be used where medical management has failed.

There is no role for nerve conduction studies in this patient. Paraesthesia are a common side effect of acetazolamide, and this patient is unlikely to tolerate an increase in the dose.

## **Intracranial venous thrombosis**

### **Overview**

- can cause cerebral infarction, much less common than arterial causes
- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

### **Features**

- headache (may be sudden onset)

- nausea & vomiting

#### Sagittal sinus thrombosis

- may present with seizures and hemiplegia
- parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

#### Cavernous sinus thrombosis

- other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

#### Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



CT with contrast demonstrating a **superior sagittal sinus thrombosis** showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

#### Question 1 of 17

A 32-year-old woman presents to clinic with a constant headache. She has attempted to control this by taking daily paracetamol, ibuprofen and codeine for the last two months. Her headache has not improved. She describes the headache as present almost every single day but is not

disabling. There is a concern that she may have a medication overuse headache. What is the most appropriate management?

[Wean off codeine18%Stop codeine abruptly7%Stop codeine and ibuprofen abruptly10%Wean off codeine and ibuprofen19%Stop all medications abruptly45%](#)

The correct answer is to stop all medications abruptly. The duration of the headache and regular use of codeine makes the diagnosis of medication overuse headache most likely. Whilst codeine and triptans are most commonly the cause, another analgesia can contribute and all of the analgesia should be stopped abruptly. Likely improvement will be seen within a few days.

## **Medication overuse headache**

Medication overuse headache is one of the most common causes of chronic daily headache. It may affect up to 1 in 50 people

### **Features**

- present for 15 days or more per month
- developed or worsened whilst taking regular symptomatic medication
- patients using opioids and triptans are at most risk
- may be psychiatric co-morbidity

### **Management (from 2008 SIGN guidelines)**

- simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- opioid analgesics should be gradually withdrawn

### **Question 2 of 17**

A 67-year-old male presents to the hospital with 2 hours of acute onset right sided weakness and speech difficulties.

A CT cerebral angiogram shows proximal left middle cerebral artery (LMCA) thrombosis.

Seven days prior to this presentation he underwent a laparotomy for bowel obstruction secondary

to an incarcerated umbilical hernia. In the absence of IV thrombolysis which of the following emergency therapies may benefit the patient?

Intra-arterial clot retrieval 62% Prasugrel 12% Mannitol 5% Intravenous heparin infusion 14% Rosuvastatin 7%

Patient's presenting with a confirmed acute proximal MCA or distal internal carotid artery or basilar artery occlusion may benefit from intra-arterial clot retrieval. Ideally, patients should undergo the procedure within 6 hours of symptom onset.

Recent abdominal surgery is an exclusion criterion for intravenous thrombolysis which is why the patient in this question may benefit from intra-arterial clot retrieval.

Three recently published randomised trials established the safety and efficacy of intra-arterial clot retrieval in addition to intravenous thrombolysis for eligible patients presenting with acute stroke. Patients who are ineligible for IV thrombolysis who present within the appropriate time-frame with large vessel occlusion may also benefit from intra-arterial clot retrieval.

All other answers have not been proven to benefit the patient in the emergency setting.

A statin based therapy should however be initiated in all ischaemic stroke patients as part of their secondary prevention regimen.

## **Stroke: management**

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy\*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'

- if the cholesterol is > 3.5 mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

## Thrombolysis

Thrombolysis should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Alteplase is currently recommended by NICE.

Contraindications to thrombolysis:

<b>Absolute</b>	<b>Relative</b>
<ul style="list-style-type: none"> <li>- Previous intracranial haemorrhage</li> <li>- Seizure at onset of stroke</li> <li>- Intracranial neoplasm</li> <li>- Suspected subarachnoid haemorrhage</li> <li>- Stroke or traumatic brain injury in preceding 3 months</li> <li>- Lumbar puncture in preceding 7 days</li> <li>- Gastrointestinal haemorrhage in preceding 3 weeks</li> <li>- Active bleeding</li> <li>- Pregnancy</li> <li>- Oesophageal varices</li> <li>- Uncontrolled hypertension &gt;200/120mmHg</li> </ul>	<ul style="list-style-type: none"> <li>- Concurrent anticoagulation (INR &gt;1.7)</li> <li>- Haemorrhagic diathesis</li> <li>- Active diabetic haemorrhagic retinopathy</li> <li>- Suspected intracardiac thrombus</li> <li>- Major surgery / trauma in preceding 2 weeks</li> </ul>

## Secondary prevention

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration

- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST\*\* criteria or > 50% according to NASCET\*\*\* criteria

\*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this

\*\*European Carotid Surgery Trialists' Collaborative Group

\*\*\*North American Symptomatic Carotid Endarterectomy Trial

### Question 3 of 17

A 53-year-old lady was admitted to the medical admission unit having presented to the Emergency Department with a severe headache which had developed over the last five days. She described the headache as a continual dull pain across the front of her head and was significantly worsened when she sat up as well as when she coughed or strained. It was alleviated only when she lied down in a dark room; paracetamol 1g QDS and ibuprofen 400mg TDS did not provide any relief. She denied the presence of nausea or vomiting, her vision was not affected and other than feeling tired she did not complain of any other symptoms. Her past medical history was comprised of non-classical migraines and hypothyroidism for which she was prescribed levothyroxine 175mcg OD. Seven days ago she was admitted with a headache, fever and photophobia; review of her medical notes revealed the following results from the previous admission:

Hb 142 g/l

Platelets  $326 \times 10^9/l$

WBC  $11.2 \times 10^9/l$

Glucose 5.4 mmol/l

ESR 32 mm/hr

CRP 46 mg/l

PTT 12.2 (NR 12-14s)

APTT 44s (NR 300-46s)

Fibrinogen 5.2 (NR 2-4 g/l)

Urine MCS: NAD

Blood MCS: NAD

CT Head: normal intracranial appearances; no space occupying lesion or haemorrhage identified

Lumbar puncture:

Protein 0.3g (NR 0.2-0.4 g/L)

Glucose 3.6 mmol/l

WCC 8 (<5/mm<sup>3</sup>)

Opening pressure 15 (NR 10-20 cmH<sub>2</sub>O)

MCS NAD

Examination revealed the presence of a female in a dark room lying flat. Her temperature was 36.6°C, heart rate 77bpm, respiratory rate 16/min and blood pressure 136/78 mmHg.

Examination her cardiovascular and respiratory systems were unremarkable. Examination of her neurological system revealed the presence of normal functioning cranial nerves 2-12 with unremarkable fundoscopy; there was no neck stiffness or photophobia objectively. There was no neck stiffness and Kernig's sign was negative. Examination of her peripheral neurological system was unremarkable.

What is the single next best management option?

[Organise urgent cranial MR venogram scan24%Organise urgent cranial MRI scan6%Commence therapy with sumatriptan12%Administer epidural blood patch50%Send CSF for xanthochromia analysis7%](#)

This lady has developed post-lumbar puncture headache (PLPH), a common complication of a lumbar puncture and is thought to be caused by excess leakage of cerebrovascular fluid causing a relatively low intracranial pressure and is aggravated significantly when assuming a non-supine posture. There are of course many other diagnoses that need to be considered, including meningitis, migraine, cortical vein thrombosis, intracerebral haemorrhage and cluster headaches. In most instances however the diagnosis of PLPH can be made clinically. Patients frequently believe the cause of their headaches is due to migraine and therefore report that avoiding bright light alleviates their headache when in fact it is lying down which is alleviating the headache. Management is conservative, including administering analgesia and sufficient fluids. If this fails to resolve the headache the gold standard management is an epidural blood patch. See <http://www.paulchristomd.com/wp-content/themes/flowhub/pdf/PostduralPunctureHA.pdf> for a comprehensive review.



## Post-lumbar puncture headache

Headache following lumbar puncture (LP) occurs in approximately one-third of patients. The pathophysiology of is unclear but may relate to a 'leak' of CSF following dural puncture. Post-LP headaches are more common in young females with a low body mass index

### Typical features

- usually develops within 24-48 hours following LP but may occur up to one week later
- may last several days
- worsens with upright position
- improves with recumbent position

### Factors which may contribute to headache      Factors which do not contribute to headache

Increased needle size  
Direction of bevel  
Not replacing the stylet  
Increased number of LP attempts

Increased volume of CSF removed  
Bed rest following procedure  
Increased fluid intake post procedure  
Opening pressure of CSF  
Position of patient

### Management

- supportive initially (analgesia, rest)
- if pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma
- treatment options include: blood patch, epidural saline and intravenous caffeine

### Question 5 of 17

A 32-year-old man with an inherited condition leading to deafness and retinitis pigmentosa, attends the genetic counselling clinic. His wife is also from the deaf community and has myopia (-2.0) requiring corrective lenses and does not have retinitis pigmentosa or a family history of blindness. She does not carry the gene of the condition described in her husband.

Regarding their children:

[25% chance of having an affected child](#)15%[50% chance of having an affected child](#)29%[100% chance of having an affected child](#)9%[50% will carry the gene but not have the condition](#)22%[100% will carry the gene but not have the condition](#)25%

The patient described has Usher's syndrome - an autosomal recessive disorder. It is the leading cause of deaf-blindness. As you have been told the wife does not have the condition nor carries the gene, so none of their children will have the condition. All children however, will inherit one healthy gene (from mother) and one defective gene (from father) - therefore becoming carriers of the condition.

Retinitis pigmentosa is the progressive degeneration of photoreceptor cells in the retina. It presents with peripheral vision loss and difficulty seeing in dim light (poor night vision as rod photoreceptors are affected first). There are lots of different mutations, and retinitis pigmentosa can be inherited in many different ways; autosomal dominant, autosomal recessive, X-linked and mitochondrial.

It can be associated with a number of rare such as:

- Usher's syndrome associated deafness
- Refsum disease associated anosmia
- Kearns-Sayre syndrome associated ophthalmoplegia

There are others but they are beyond the scope of the MRCP examination.

## **Retinitis pigmentosa**

Retinitis pigmentosa primarily affects the peripheral retina resulting in tunnel vision

### **Features**

- night blindness is often the initial sign
- tunnel vision due to loss of the peripheral retina (occasionally referred to as funnel vision)
- fundoscopy: black bone spicule-shaped pigmentation in the peripheral retina, mottling of the retinal pigment epithelium

### **Associated diseases**

- Refsum disease: cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome

- Alport's syndrome



Image sourced from [Wikipedia](#)



Fundus showing changes secondary to retinitis pigmentosa

#### Question 6 of 17

A 32 year old female is referred for a neurological opinion. She describes two separate occasions within the last six months of unilateral blurred visual loss. Her symptoms developed over a few days, comprising blurring of the vision and pain, particularly on eye movement. On both occasions this peaked within three days then gradually resolved over two weeks. Lumbar puncture reveals elevated protein level and CSF pleocytosis. Serum Aquaporin-4 is positive. What is the most likely diagnosis?

[Multiple sclerosis](#)12% [Neuromyelitis optica](#)73% [Leptomeningeal gliomatosis](#)5% [Myasthenia gravis](#)5% [Idiopathic intracranial hypertension](#)5%

Her symptoms are highly suggestive of Neuromyelitis optica (NMO, also known as Devic disease). NMO causes demyelination of the optic nerves or spinal cord due to autoimmune inflammation. Aquaporin-4 (AQP-4) is a water channel protein located in the astrocytic foot processes; NMO-IgG antibody attacks AQP-4 causing demyelination.

NMO typically presents with episodes of optic neuritis or transverse myelitis. The optic neuritis can be clinically indistinguishable from that seen in multiple sclerosis (MS), whereas the transverse myelitis is commonly more of a complete picture than that of MS. This is a result of the fact that the resulting spinal cord demyelination seen in NMO is longer and more extensive.

## **Neuromyelitis optica**

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder. Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations<sup>1</sup>. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis requires bilateral optic neuritis, myelitis and 2 of the following 3 criteria<sup>2</sup>:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

1. Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. *Lancet Neurol.* 2007;6(9):805.

2. Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485.

### **Question 2 of 7**

A 70-year-old man with hypertension and previous myocardial infarction 3 years ago presents to his GP with a 2 day history of a painful vesicular rash over his left chest and back. It is well demarcated and confined to the T6 dermatome. His GP diagnoses shingles and prescribes pain relief. His rash resolves gradually over the next 2 weeks.

Four weeks later the man develops chest pain on the left side which is stabbing in shooting in nature. He attends the Emergency Department. On examination his blood pressure is 154/96 mmHg and heart rate is 50/min and oxygen saturations on room air 98%.

His investigations results were as follows:

Chest x-ray: No abnormalities.

ECG: 50/min. PR interval 230 milliseconds. QRS interval 110 milliseconds. 5 millimetre Q waves in the inferior leads. Normal T wave and ST segments.

His d-dimer and 12 hour troponin are both normal.

Which analgesic agent is contraindicated?

[Amitriptyline55%Duloxetine18%Gabapentin9%Oxycodone9%Pregabalin9%](#)

This gentleman has post-herpetic neuralgia causing his chest pain.

He has a history of heart attack and his ECG shows evidence of inferior myocardial infarction in the territory of the right coronary artery. This has resulted in a first degree heart block as evidenced by the long PR interval.

NICE Guidance on Neuropathic Pain (CG173) advocates a choice of amitriptyline, duloxetine, gabapentin or pregabalin. According to the BNF amitriptyline is contraindicated in arrhythmias particularly heart block, as in this case. It is also contraindicated in the recovery period following myocardial infarction, though this gentleman is outside of this.

## **Tricyclic antidepressants**

Tricyclic antidepressants (TCAs) are used less commonly now for depression due to their side-effects and toxicity in overdose. They are however used widely in the treatment of neuropathic pain, where smaller doses are typically required.

Common side-effects

- drowsiness
- dry mouth
- blurred vision
- constipation
- urinary retention

Choice of tricyclic

- low-dose amitriptyline is commonly used in the management of neuropathic pain and the prophylaxis of headache (both tension and migraine)
- lofepramine has a lower incidence of toxicity in overdose
- amitriptyline and dosulepin (dothiepin) are considered the most dangerous in overdose

### More sedative Less sedative

Amitriptyline	Imipramine
Clomipramine	Lofepramine
Dosulepin	Nortriptyline
Trazodone*	

\*trazodone is technically a 'tricyclic-related antidepressant'

### Question 3 of 7

A 28-year-old female presents to the emergency department with a severe headache and lethargy. The headache came on fairly quickly whilst she was watching television. She is otherwise fit and well, has no medical problems and takes no regular medications. She lives at home with her husband and two-year-old daughter. Whilst in the emergency department she is given two co-codamol for her persisting headache but then vomits. On examination, there is no focal neurology but she is slightly drowsy and her GCS is 14/15.

Hb	126 g/l
Platelets	274 * 10 <sup>9</sup> /l
WBC	10.9 * 10 <sup>9</sup> /l
Na <sup>+</sup>	124 mmol/l
K <sup>+</sup>	5.0 mmol/l
Urea	4.1 mmol/l
Creatinine	124 µmol/l

What is the most likely diagnosis?

[Tension headache6%](#) [Addison's disease14%](#) [Pituitary apoplexy52%](#) [Sub-arachnoid haemorrhage23%](#) [Cranial diabetes insipidus6%](#)

A sudden onset headache with altered consciousness and vomiting is very suspicious for an intracranial event such as a subarachnoid bleed. The hyponatraemia, in this case, would not be explained by a sub-arachnoid haemorrhage alone however. Bleeding into, or from, a pituitary adenoma can cause features similar to an aneurysmal subarachnoid bleed. It might, as in this case, cause secondary hypoadrenalism which would explain the hyponatraemia. One would expect hypernatraemia with diabetes insipidus.

## Pituitary apoplexy

Sudden enlargement of pituitary tumour secondary to haemorrhage or infarction

Features

- sudden onset headache similar to that seen in subarachnoid haemorrhage
- vomiting
- neck stiffness
- visual field defects: classically bitemporal superior quadrantic defect
- extraocular nerve palsies
- features of pituitary insufficiency e.g. Hypotension secondary to hypoadrenalism

Question 4 of 7

A 64 year old man is referred to you from a psychiatrist for a second opinion. He initially presented with a 3 month history of low mood, apathy and suicidal ideation. In addition he was asked to retire early from his job as an accountant as he was performing poorly at work. He is also sleeping an average of 14 hours per day.

When the psychiatrist assessed him he noted abnormal jerky movements in the lower limbs as well as a broad based gait. An MMSE was performed and he scored 15/30. This is corroborated by your examination and you also note hyperreflexia in the lower limbs and nystagmus.

He has no history of cognitive impairment or any psychiatric history. There is no family history of any neurological or psychiatric conditions and his only past medical history is an appendectomy 20 years ago which was complicated by a large intraperitoneal bleed.

Which findings are you most likely to find on investigation?

Increased T2 and FLAIR signal intensity in the putamen and head of the caudate on T2 weighted MRI, 14-3-3 protein on CSF49%CAG trinucleotide repeats on the short arm of chromosome 415%Increased T2 and FLAIR signal intensity in the putamen and head of caudate on T2 weighted MRI and oligoclonal bands on CSF12%CAG trinucleotide repeats on the short arm of chromosome 1212%Cortical atrophy, most prominent in the frontal lobes13%

The diagnosis here is Sporadic Creutzfeldt Jakob Disease. CJD is characterised by a rapidly progressive dementia along with neuropsychiatric changes. Death usually occurs within a year of diagnosis. Most common psychiatric symptoms are depression and apathy although euphoria,

anxiety and emotional lability can also be seen. Myoclonus, ataxia, nystagmus and hyperreflexia are the most common neurological symptoms.

A represents the most likely findings for sporadic CJD. Sporadic CJD normally has a longer clinical course than nvCJD and is normally seen in older people (although nvCJD is possible in this individual as he may have had a blood transfusion 20).

B represents a finding seen in Huntingtons chorea. The lack of family history makes this diagnosis less likely. The oligoclonal bands in C are seen in association with Multiple Sclerosis not CJD. D is not a recognised investigation finding and E would be more consistent with a diagnosis of Picks Disease. The very rapid onset of symptoms and presence of myoclonic jerks make this answer less likely.

## **Creutzfeldt-Jakob disease**

Creutzfeldt-Jakob disease (CJD) is rapidly progressive neurological condition caused by prion proteins. These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.

### Features

- dementia (rapid onset)
- myoclonus

### Investigation

- CSF is usually normal
- EEG: biphasic, high amplitude sharp waves (only in sporadic CJD)
- MRI: hyperintense signals in the basal ganglia and thalamus

### Sporadic CJD

- accounts for 85% of cases
- 10-15% of cases are familial
- mean age of onset is 65 years

### New variant CJD



- younger patients (average age of onset = 25 years)
- psychological symptoms such as anxiety, withdrawal and dysphonia are the most common presenting features
- the 'prion protein' is encoded on chromosome 20 - its role is not yet understood
- methionine homozygosity at codon 129 of the prion protein is a risk factor for developing CJD - all patients who have so far died have had this
- median survival = 13 months

#### Other prion diseases

- kuru
- fatal familial insomnia
- Gerstmann Straussler-Scheinker disease

#### Question 6 of 7

A 17-year-old man is referred by the emergency department with weakness of his lower limbs and hands, worsening over the last 2 days. He is having increasing difficulty walking and is becoming very clumsy and dropping things. He burnt his hand yesterday in the kitchen without realising until afterwards that he had done it. He also complains of feeling dizzy on standing but has no chest pain or palpitations. He is normally fit and well, although did suffer a bout of diarrhoea and vomiting 4 weeks ago. He is on no regular medication and denies any alcohol or smoking history.

On examination he is afebrile, his blood pressure is 128/79 mmHg on lying but on standing it drops to 90/60 mmHg. His respiratory rate is 20/min and his saturations are 97% on air. His cardiovascular, respiratory and abdominal examinations are normal. Neurological examination reveals symmetrical distal weakness of his lower limbs with relative proximal sparing and altered sensation to fine touch, vibration and proprioception. He has similar findings in his upper limbs. He is suspected of having Guillain-Barre syndrome and following blood tests, CT head and lumbar puncture is started on IV immunoglobulins. Despite this, he begins to become increasingly short of breath and he is referred to ITU for respiratory support.

What respiratory parameter is used to determine if invasive ventilator support is needed?

[pO<sub>2</sub> on ABG < 8kPa 11% FEV<sub>1</sub>:FVC ratio < 0.78% Saturations on 15 litres O<sub>2</sub> less than 93% 6% FVC < 15ml/kg 64% Peak flow of less than 300ml 12%](#)

This man has Guillain-Barre syndrome with autonomic involvement and compromise to his respiratory function. The parameter used to assess whether a patient needs ventilator support is an FVC <15-20ml/kg. low pO<sub>2</sub>, low saturations and low peak flow are all indicators of poor respiratory function but FVC is the parameter used in these cases. FEV<sub>1</sub>:FVC ratio is not used.

## Guillain-Barre syndrome: management

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically *Campylobacter jejuni*).

### Management

- plasma exchange
- IV immunoglobulins (IVIG): as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function

### Prognosis

- 20% suffer permanent disability, 5% die

### Question 7 of 7

A 52-year-old male presents to the emergency department with a 5-week history of constipation not relieved by over the counter laxatives. His past medical history was significant for hypertension, COPD and schizophrenia. His current medications include ramipril, clozapine and tiotropium. He denied weight loss, poor appetite or other alarming symptoms. His family history was significant for bowel cancer with his father and uncle having died of colon cancer aged 78 and 82 respectively. His sister had a hysterectomy at the age of 72 but he was not sure why. On examination, his blood pressure was 124/78mmHg lying and 115/80mmHg standing. Pulse was 63/min. Clinical examination did not reveal any significant findings.

### Investigations:

Hb	137 g/l
MCV	82 fl
Platelets	$420 \times 10^9/l$
WBC	$7 \times 10^9/l$
Creatinine	89 $\mu\text{mol/L}$
Urea	4.7 $\mu\text{mol/L}$

Na+ 143 mmol/L  
K+ 3.9 mmol/L  
Corrected Calcium 2.3mmol/L  
FOB negative  
Abdominal X-ray faecal loading

What is the most likely cause of constipation in this case?

[Clozapine68%Colon cancer10%Illicit drugs6%Dehydration10%Malingering5%](#)

This is an interesting case and the differential is between colon cancer and clozapine-induced constipation. Clozapine is reserved for drug-resistant schizophrenia and rightfully so as it comes with serious side effects one of which is constipation.

Constipation occurs in 14% of people on clozapine and it is believed to be an anticholinergic effect. There are papers in literature which report more serious implications like bowel infarction and death from longstanding clozapine-induced constipation.

Cancer is unlikely here as this patient has no other alarming symptoms or signs (no weight loss, normal haemoglobin, negative FOB) to suggest this and also the cancer cases in his family history are unlikely due to a hereditary condition as it has appeared in elderly relatives with no evidence of anticipation. In practice though cancer should be excluded.

There is no indication of illicit drug use and dehydration is unlikely to cause such long history of constipation without physical findings. Here we are not told of any finding suggesting dehydration on clinical examination. Malingering usually indicates personal gains of which there are not mentioned.

Clozapine is a common cause of constipation and should not be ignored. The above case is a good example.

Death From Clozapine-Induced Constipation Case Report and Literature Review  
<http://psychrights.org/research/digest/nlps/DeathbyClozapineConstipation.pdf>

Clozapine-induced Bowel Infarction A Case Report Nicholas D. McKinnon, MD, CAPT, USAF, MC,corresponding author Alvi Azad, DO, CAPT, USAF, MC, Brian M Waters, MD, CAPT, USAF, MC, and Kaustubh G. Joshi, MD, MAJ, USAF, MC, FS  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719458/>

Pharmacy update: Clozapine-induced constipation <http://www.bsmhft.nhs.uk/gps-and-commissioners/gpmatters/issue-27-october-2013/pharmacy/>

Death from clozapine-induced constipation prompts warning <http://www.pharmaceutical-journal.com/news-and-analysis/news/death-from-clozapine-induced-constipation-prompts-warning/11100557.article>

## **Atypical antipsychotics**

Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines. The main advantage of the atypical agents is a significant reduction in extra-pyramidal side-effects.

### **Adverse effects of atypical antipsychotics**

- weight gain
- clozapine is associated with agranulocytosis (see below)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

### **Examples of atypical antipsychotics**

- clozapine
- olanzapine
- risperidone
- quetiapine
- amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication

### **Adverse effects of clozapine**

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients

Question 1 of 101

A 23-year-old comes in with a painful right knee. He denies any specific trauma. He has no past medical history. On examination, he has a red and warm knee with a moderate effusion. His observations show a respiratory rate of 24/min, blood pressure 120/72 mmHg, temperature 37.8°C. His knee is aspirated which is cloudy in appearance. Laboratory testing shows calcium pyrophosphate crystals and the Gram stain is awaited. What is the most appropriate treatment plan?

[Admit for intravenous antibiotics42%](#)[Home with analgesia18%](#)[Admit awaiting cultures15%](#)[Check ferritin18%](#)[Intra-articular depo-medrone8%](#)

Septic arthritis has not been ruled out until there are no organisms seen. The patient should be treated with intravenous antibiotics as soon as the aspirate has been taken and only be discharged once it is confirmed that they do not have septic arthritis.

Although calcium pyrophosphate crystals are most associated with pseudo gout they do not rule out septic arthritis. The ferritin would be raised in septic arthritis so using it as a screen for haemochromatosis would not be advisable in this setting.

## Septic arthritis

### Overview

- most common organism overall is *Staphylococcus aureus*
- in young adults who are sexually active *Neisseria gonorrhoeae* should also be considered

### Management

- synovial fluid should be obtained before starting treatment
- intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic
- antibiotic treatment is normally be given for several weeks (BNF states 6-12 weeks)
- needle aspiration should be used to decompress the joint
- arthroscopic lavage may be required

### Question 2 of 101

A 47-year-old lady presented with a three-week history of pain in her fingers. She had noticed her hands were getting extremely cold when she went outside and turned a 'funny colour'. When she came back inside her hands were very painful as they began to warm up. She had managed in the past by wearing gloves outside but now had ulcers on her fingertips which she had never experienced before. She also complained of epigastric pain and had longstanding shortness of breath.

Her past medical history included pulmonary fibrosis and hypertension. Her medications included propranolol, amlodipine, simvastatin and omeprazole.

On examination the skin over her hands was dry and shiny and there was severe digital ulceration on three fingertips of the left hand. There was no exudate or erythema. The fingertips were dusky in colour and extremely tender. The skin over the upper arms and chest appeared normal. On auscultation of the lungs there were fine bibasal inspiratory crepitations which did not alter in character upon coughing. Heart sounds were normal with no added murmurs. There was a left ventricular heave

**Which of the following is the most appropriate management plan for this lady?**

[Start flucloxacillin and stop all anti-hypertensive medications5%](#)[Educate this lady about the use of gloves and hand-warmers and increase her amlodipine dose18%](#)[Stop amlodipine and refer for an urgent dermatology assessment7%](#)[Stop propranolol and admit for an iloprost infusion48%](#)[Start high dose oral prednisolone22%](#)

This patient has secondary Raynauds associated with an underlying diagnosis of Limited Systemic Sclerosis. Her disease is 'limited' as opposed to 'diffuse' as she does not have skin changes proximal to the elbows. She clearly has systemic involvement with pulmonary fibrosis and oesophageal dysmotility (she has epigastric pain and is taking omeprazole). Other features that were not mentioned in the question but may be present in such patients include telangiectasia, typically over mucosal surfaces, a 'beak-like' nose and microstomia, calcinosis and renal impairment.

Severe digital ulceration in such patients can be treated with infusion of a prostacyclin analogue such as iloprost. Prompt treatment is required to avoid gangrene and loss of digits. Drugs such as beta blockers and the oral contraceptive pill can exacerbate Raynauds phenomenon by causing vascular spasm and should therefore be avoided.

There is no indication for flucloxacillin if the ulcers are not infected.

Gloves and hand-warmers can be very helpful for patients with Raynauds phenomenon. Calcium channel blockers such as amlodipine and nifedipine cause vasodilation in peripheral arterioles

are also used to treat Raynauds phenomenon. However, if there is severe ulceration admission for an iloprost infusion is required.

## **Raynaud's**

Raynaud's phenomena may be primary (Raynaud's disease) or secondary (Raynaud's phenomenon)

Raynaud's disease typically presents in young women (e.g. 30 years old) with symmetrical attacks

Factors suggesting underlying connective tissue disease

- onset after 40 years
- unilateral symptoms
- rashes
- presence of autoantibodies
- features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages
- digital ulcers, calcinosis
- very rarely: chilblains

Secondary causes

- connective tissue disorders: scleroderma (most common), rheumatoid arthritis, SLE
- leukaemia
- type I cryoglobulinaemia, cold agglutinins
- use of vibrating tools
- drugs: oral contraceptive pill, ergot
- cervical rib

Management

- first-line: calcium channel blockers e.g. nifedipine
- IV prostacyclin infusions: effects may last several weeks/months

### Question 3 of 101

A 67-year-old gentleman presents to the emergency department with a stiff and painful shoulder. He denies any trauma. He has been struggling to use his left shoulder for several weeks, finding pain that is worse at night and stiffness that has become progressively debilitating. He lives alone and has found that he now struggles with daily activities such as preparing food, and has not found over the counter medications to help. He has a past medical history of type 2 diabetes mellitus, recurrent gout, hypertension, previous TIA and an enlarged prostate. He takes metformin, allopurinol, amlodipine, ramipril, aspirin and tamsulosin. On examination, he has pain and a reduced range of motion in both passive and active ranges of the left shoulder, but the right shoulder is unaffected. **What investigation is required to establish a diagnosis?**

[Shoulder X-ray22%Shoulder MRI28%Shoulder arthroscopy5%Shoulder aspiration5%No investigation is needed for diagnosis39%](#)

Adhesive capsulitis is a clinical diagnosis and does not need imaging or arthroscopy to confirm the diagnosis

This patient has adhesive capsulitis. This is a clinical diagnosis based on the history and examination findings, especially a global reduction of movement in a shoulder on both passive and active motion. Shoulder X-ray can help exclude osteoarthritic changes, which are unlikely in this degree of debilitating stiffness and acute onset. Whilst many patients in this situation would undergo an X-ray this is not necessary in the absence of trauma, deformity or a chronic history suggestive of osteoarthritis. MRI of the shoulder is useful in diagnosing rotator cuff pathology and tendinopathy, but the clinical picture does not support this as there is global loss and the fact that the passive range of motion is affected as well. This would not be expected in rotator cuff pathology. Shoulder aspiration is useful in gout or septic arthritis, but in a patient who does not have a swollen and hot joint and who is systemically well this is unnecessary.

### **Adhesive capsulitis**

Adhesive capsulitis (frozen shoulder) is a common cause of shoulder pain. It is most common in middle-aged females. The aetiology of frozen shoulder is not fully understood.

#### Associations

- diabetes mellitus: up to 20% of diabetics may have an episode of frozen shoulder

#### Features typically develop over days

- external rotation is affected more than internal rotation or abduction



- both active and passive movement are affected
- patients typically have a painful freezing phase, an adhesive phase and a recovery phase
- bilateral in up to 20% of patients
- the episode typically lasts between 6 months and 2 years

## Management

- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral corticosteroids and intra-articular corticosteroids

## Question 4 of 101

A 58-year-old man presents with malaise and fever. He states that he has been feeling unwell for several months. His main complaints are intermittent swelling and pain of his right ear, painful red eyes, and arthralgia. He has no past medical history and takes no regular medicines.

**On examination,** you note right auricular swelling, bilateral anterior uveitis, and a symmetrical small joint polyarthritis.

Hb	115 g/l	Na <sup>+</sup>	138 mmol/l
Platelets	330 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.2 mmol/l
WBC	13.1 * 10 <sup>9</sup> /l	Urea	6.2 mmol/l
Neuts	10.4 * 10 <sup>9</sup> /l	Creatinine	95 µmol/l
Lymphs	2.5 * 10 <sup>9</sup> /l	CRP	132 mg/l
Eosin	0.6 * 10 <sup>9</sup> /l	pANCA	negative
C3	normal	C4	normal
ANA	negative	Anti Sm	negative
RhF	positive	Anti CCP	negative

**What is the most likely diagnosis?**

[Eosinophilic granulomatosis with polyangiitis9%](#)[Granulomatosis with polyangiitis12%](#)[Systemic lupus erythematosus5%](#)[Rheumatoid arthritis16%](#)[Relapsing polychondritis58%](#)

Relapsing polychondritis is a multi-systemic condition which most commonly causes relapsing episodes of auricular chondritis

Relapsing polychondritis is a multi-systemic condition characterised by repeated episodes of inflammation and deterioration of cartilage. It is often a painful disease which can cause joint deformity and be life-threatening if the respiratory tract, heart valves, or blood vessels are

affected. The exact mechanism is poorly understood, but it is thought to be related to an immune-mediated attack on cartilage proteins.

The history in this case is suggestive of relapsing polychondritis, however the clinical features are non-specific and can occur due to many of the other options. The laboratory data is therefore of great use in narrowing down the differential diagnosis.

A normal C3 and C4, and negative ANA, make SLE unlikely.

A negative pANCA and cANCA makes granulomatosis with polyangitis and eosinophilic granulomatosis less likely.

A negative anti-CCP makes rheumatoid arthritis less likely. Although RF is positive, this is very non-specific and is positive in many other diseases and in the healthy general population.

## **Relapsing polychondritis**

Relapsing polychondritis is a multi-systemic condition characterised by repeated episodes of inflammation and deterioration of cartilage. This most commonly affects the ears, however can affect other parts of the body such as the nose and joints.

Key features:

- Ears: auricular chondritis, hearing loss, vertigo
- Nasal: nasal chondritis
- Ocular: episcleritis, scleritis, iritis, and keratoconjunctivitis sicca
- Joints: arthralgia
- Less commonly: cardiac valvular regurgitation, cranial nerve palsies, peripheral neuropathies, renal dysfunction

Diagnosis:

- Various scoring systems based on clinical, pathological, and radiological criteria

Treatment

- Induce remission: steroids
- Maintenance: azathioprine, methotrexate, cyclosporin, cyclophosphamide

Question 5 of 101

A 40-year-old man is investigated for back. For the past few months he has been troubled with pain in his lower back which is typically worse in the morning and better by the end of the day. There is some radiation of pain to the right buttock but no leg pains. An x-ray of his lumbar spine is shown below



© Image used on license from [Radiopaedia](#)



**What is the most likely cause of his back pain?**

[Lumbar disc prolapse at multiple levels](#)3%[Osteopetrosis](#)5%[Calcification of the vertebral artery](#)5%[Spinal stenosis](#)4%[Ankylosing spondylitis](#)83%

This image shows the typical appearance of bamboo spine with a single central radiodense line

related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints.

Note the history of morning pain is typical for an inflammatory arthritis such as ankylosing spondylitis.

## **Ankylosing spondylitis: investigation and management**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

### **Investigation**

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



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40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



© Image used on license from [Radiopaedia](#)



Ankylosing spondylitis with well formed syndesmophytes



© Image used on license from [Radiopaedia](#)



Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



© Image used on license from [Radiopaedia](#)



Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease





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Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

## Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement

- the 2010 EULAR guidelines suggest: '*Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments*'
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

#### Question 6 of 101

A 38-year-old male plumber is referred to the medical assessment unit by his GP due to reduced oxygen saturations. He has had mild asthma since childhood but no other medical history of note. His medications are a salbutamol inhaler when required and co-codamol for long standing back pain. **On examination** he is found to have an early diastolic murmur but no other abnormalities are detected. He goes on to have a chest x-ray which demonstrates apical interstitial shadowing. He undergoes pulmonary function tests which are as follows:

FEV1	1.9L (Predicted 2.1-3.1)
FVC	2.2 (Predicted 3.0-4.4)
TLC	4.5 (Predicted 5.0-7.5)

Transfer factor (DLCO) Low

**What is the most likely diagnosis?**

[Ankylosing spondylitis69%](#) [Asbestosis8%](#) [Extrinsic allergic alveolitis11%](#) [Churg-Strauss syndrome6%](#) [Sarcoidosis5%](#)

There are a couple of red-herrings in this question designed to lead candidates astray. The fact that he is a plumber could be linked to a diagnosis of asbestosis, whilst his prior history of asthma may be suggestive of Churg-Strauss syndrome. However the fact that this patient's CXR shows apical interstitial shadowing, combined with the restrictive pattern of his pulmonary function tests indicate that he is suffering with apical lung fibrosis. This narrows the potential answers down to ankylosing spondylitis, sarcoidosis or extrinsic allergic alveolitis. The history of back pain and the finding of an early diastolic murmur (suggestive of aortic regurgitation) confirm ankylosing spondylitis as the most likely diagnosis.

#### **Ankylosing spondylitis: features**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in

males (sex ratio 3:1) aged 20-30 years old.

### Features

- typically a young man who presents with lower back pain and stiffness of insidious onset
- stiffness is usually worse in the morning and improves with exercise
- the patient may experience pain at night which improves on getting up

### Clinical examination

- reduced lateral flexion
- reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- reduced chest expansion

### Other features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis
- and cauda equina syndrome
- peripheral arthritis (25%, more common if female)

### Question 2 of 99

A 72-year-old woman comes to the rheumatology clinic for review. She has suffered from polymyalgia rheumatica over the past year, which has been treated with oral prednisolone, and she is unable to reduce her dose below 10mg per day without a return of her symptoms. On examination her blood pressure is 155/100 mmHg, her pulse is 72 beats per minute and regular, she has truncal obesity and her body mass index is 31 kg/m<sup>2</sup>.

### Investigations

ESR 44 mm/hr

Which of the following is the most effective steroid-sparing option for this patient?

[Methotrexate23%Infliximab0%Tocilizumab23%Azathioprine36%Hydroxychloroquine18%](#)

Tocilizumab is the agent with the best evidence for steroid sparing in patients with polymyalgia rheumatica

Tocilizumab is an anti-IL6 monoclonal antibody which was originally developed for the treatment of rheumatoid arthritis. In patients with a history of polymyalgia rheumatica, when added to prednisolone versus placebo, tocilizumab is associated with a remission rate above 50%, versus a remission rate of 18% over 1 year in patients treated with corticosteroids alone. It, therefore, represents the most effective disease-modifying agent in polymyalgia.

Infliximab is not effective in treating polymyalgia, methotrexate is the mainstay of steroid-sparing therapy in rheumatoid arthritis, and hydroxychloroquine is used in the treatment of lupus. Azathioprine is the traditional steroid-sparing agent used for treating polymyalgia, although it is associated with a very modest improvement in remission rates versus corticosteroids alone.

<http://www.nejm.org/doi/full/10.1056/NEJMoa1613849>

## **Polymyalgia rheumatica**

### Pathophysiology

- overlaps with temporal arteritis
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

### Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- aching, morning stiffness in proximal limb muscles (not weakness)
- also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

### Investigations

- ESR > 40 mm/hr
- note CK and EMG normal
- reduced CD8+ T cells

## Treatment

- prednisolone e.g. 15mg/od - dramatic response

### Question 1 of 99

A 52-year-old female presents to rheumatology outpatient clinic with three months history of severe pain on her hands. She has no significant past medical history. On examination, there are swelling and erythema of the first, second and third metacarpophalangeal joints on both hands. She is diagnosed with rheumatoid arthritis.

CRP 34mg/L

What treatment should be started?

[Methotrexate26%](#) [Infliximab3%](#) [Methotrexate, prednisolone and sulfasalazine56%](#) [Sulfasalazine and prednisolone12%](#) [Azathioprine3%](#)

Patients with newly diagnosed rheumatoid arthritis and evidence of active exacerbation should be treated with methotrexate and another DMARD plus steroid. Options for other DMARDs include sulfasalazine, leflunomide and hydroxychloroquine. DMARD monotherapy is only used if the combination therapy is not appropriate. There is no indication why this patient can't have DMARD combination therapy. Biological agents such as infliximab is not used as a first line medication for patients with rheumatoid arthritis.

## Rheumatoid arthritis: management

The management of rheumatoid arthritis (RA) has been revolutionised by the introduction of disease-modifying therapies in the past decade. NICE has issued a number of technology appraisals on the newer agents and released general guidelines in 2009.

Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible. Other important treatment options include analgesia, physiotherapy and surgery.

## Initial therapy

- in the 2009 NICE guidelines it is recommended that patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)

## DMARDs

- methotrexate is the most widely used DMARD. Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- sulfasalazine
- leflunomide
- hydroxychloroquine

## TNF-inhibitors

- the current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- etanercept: recombinant human protein, acts as a decoy receptor for TNF- $\alpha$ , subcutaneous administration, can cause demyelination, risks include reactivation of tuberculosis
- infliximab: monoclonal antibody, binds to TNF- $\alpha$  and prevents it from binding with TNF receptors, intravenous administration, risks include reactivation of tuberculosis
- adalimumab: monoclonal antibody, subcutaneous administration

## Rituximab

- anti-CD20 monoclonal antibody, results in B-cell depletion
- two 1g intravenous infusions are given two weeks apart
- infusion reactions are common

## Abatacept

- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion
- not currently recommended by NICE

### Question 3 of 99

A 27-year-old male presents after recently returning from Bangladesh with 2 weeks of daily spiking fever, a new rash on his foot and pain on bending his knees or closing his hands. He also reports lumps and bumps on his neck that he thinks are new. He denies any cough or weight loss. He has no other past medical history and is unaware of any unwell family members. On examination, his temperature is 39.2 degrees. You note a maculopapular rash on his left sole and face. His knees and wrists are swollen and tender. His chest and cardiovascular examination are unremarkable, his abdomen is soft. However, you note a 12cm splenomegaly. His serum tests demonstrate:

Hb 127 g/l

Platelets  $450 \times 10^9/l$

WBC  $17.0 \times 10^9/l$

Neuts  $11.0 \times 10^9/l$

Na<sup>+</sup> 138 mmol/l

K<sup>+</sup> 3.5 mmol/l

Urea 7.8 mmol/l

Creatinine 70  $\mu$ mol/l

CRP 30 mg/l

Ferritin 2000  $\mu$ g/l

ALP 250 u/l

ALT 160 u/l

ANA negative

dsDNA negative

His chest radiograph appears unremarkable with no focal consolidation. A first induced sputum is negative for acid-fast bacilli. What is the most likely diagnosis?

[Miliary tuberculosis6%Adult onset Stills disease68%Reactive arthritis post-travellers diarrhoea13%Porphyria cutanea tarda9%Systemic lupus erythematosus4%](#)

Adult onset Stills disease (ASD) is a systemic inflammatory condition of unknown aetiology but often thought to be secondary to an infectious trigger on a background of genetic predisposition. It classically presents in young adults under 40 years old, peaking between 15-25 years, with a daily fever and a new non-pruritic rash. The most sensitive diagnostic classification is the Yamaguchi criteria<sup>1</sup>. defined by a patient presenting with all major criteria and at least two minor criteria.

Major criteria:

- Fever greater than 39 degrees over one week
- Arthralgia or arthritis lasting two weeks or longer
- Non-pruritic or maculopapular rash, salmon coloured, found on trunk or extremities, particularly during febrile episodes
- Leucocytosis >10,000/microL

Minor criteria:

- Sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, negative ANA or rheumatoid factor

A number of features in the history and examination should point you towards ASD. The nature of the fever is quotidian: ASD fevers tend to spike daily or twice daily. Secondly, the location of the rash is also characteristic, most commonly a salmon coloured rash in the trunk or the soles, palms and face. Knees, wrist and ankles are the most common sites for arthritis and arthralgias. Ferritin rises are characteristic of ASD, observed in up to 70% of patients<sup>2</sup>. Mild elevations in ALT and ALP are also characteristic of ASD. However, the patient does not describe a sore throat, which is often severe and non-suppurative in up to 70% of ASD patients. Treatment of ASD involves systemic immunosuppression, initially with prednisolone followed by DMARDs.

The main differential to consider is TB. A two-week history is short for miliary TB and particularly unusual for someone without chest signs. It typically is the result of a pulmonary focus eroding the pulmonary vein, leading to systemic dissemination. A negative induced sputum also points against miliary Tb but does not fully exclude it. SLE could also fit with the clinical picture but again, less likely with negative dsDNA and ANA. There is no suggestion that the patient has recently had GI symptoms. Reactive arthritis, formerly known as Reiter's syndrome, does not account for the splenomegaly or serum abnormalities.

1. Yamaguchi M, Ohta A, Tsunematsu T et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19(3):424
2. Ohta A, Yamaguchi M, Tsunematsu T et al. Adult Still's disease: a multicenter survey of Japanese patients. J Rheumatol. 1990;17(8):1058

## **Still's disease in adults**

Adult Still's disease

- typically affects 16-35 year olds



## Features

- arthralgia
- elevated serum ferritin
- rash: salmon-pink, maculopapular
- pyrexia
- lymphadenopathy
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

## Question 4 of 99

A 72-year-old man presents by blue light ambulance to the emergency department. He has been increasingly drowsy over the past 4 days and has not been out of bed for the past 48 hours. His wife reports two episodes of sweating and a high temperature during this period. He has been admitted three times in the last 9 months with urinary tract infections and is awaiting a transurethral resection of his prostate for benign prostatic hypertrophy. His other past medical history includes type 2 diabetes mellitus, diagnosed 4 years ago, and rheumatoid arthritis diagnosed 16 years ago. His wife tells you that he appears to be prone to infections over the past few years. He normally walks with a stick but his exercise tolerance has been decreasing since doctors told him that he had 'scarring of his lungs from his rheumatoid.' On examination, he is sleepy but easily rousable and orientated to time and place. He is cool peripherally, with dry mucous membranes and JVP +1cm above the angle of Louis. Blood pressure measures 82/55mmHg, heart rate is 105/minute. You note conjunctival pallor, bilateral ulnar deviation of his hands, an inflamed second MTP joint and nodules beneath both elbows. Auscultation of the chest demonstrates bibasal inspiratory fine crackles. Abdominal examination demonstrates a 2cm liver edge and a 13cm spleen. Neurological examination is unremarkable. Routine blood tests and blood cultures are taken. What is the most appropriate treatment?

[Oral antibiotics as per local guidelines for mild-moderate community acquired pneumonia4%](#)  
[Intravenous antibiotics as per local guidelines for severe community acquired pneumonia11%](#)  
[Intravenous antibiotics as per local guidelines for urosepsis17%](#)  
[Intravenous antibiotics as per local guidelines for intra-abdominal sepsis6%](#)  
[Intravenous antibiotic as per local guidelines for neutropenic sepsis61%](#)

The patient is known to have rheumatoid arthritis with multiple extra-articular features. He is also clinically septic and intravascularly dehydrated. The proneness to infections must raise suspicions of neutropenia, combining with RA with extra-articular features, splenomegaly to produce the classic triad of Felty's syndrome. Although he has had multiple episodes of previous UTIs, the history is unclear here. Neutropenic sepsis without a clear source of infection must be treated with intravenous antibiotics as per local guidelines.

## Rheumatoid arthritis: complications

A wide variety of extra-articular complications occur in patients with rheumatoid arthritis (RA):

- respiratory: pulmonary fibrosis, pleural effusion, pulmonary nodules, bronchiolitis obliterans, methotrexate pneumonitis, pleurisy
- ocular: keratoconjunctivitis sicca (most common), episcleritis, scleritis, corneal ulceration, keratitis, steroid-induced cataracts, chloroquine retinopathy
- osteoporosis
- ischaemic heart disease: RA carries a similar risk to type 2 diabetes mellitus
- increased risk of infections
- depression

Less common

- Felty's syndrome (RA + splenomegaly + low white cell count)
- amyloidosis

Question 5 of 99

A 64-year-old male presents with known lumbosacral poly-radiculopathy caused by neurosarcoidosis is on immunosuppression with high dose steroids for several months and methotrexate. He is admitted with breathlessness and a dry cough. He is found to have a type 1 respiratory failure. A CT chest shows ground glass shadowing suggesting *Pneumocystis jirovecii* pneumonia. You discuss with the microbiology team who suggest also covering the patient for a bacterial pneumonia and viral pneumonitis.

Which of the following medications could have a potentially life threatening interaction with his current medications?

[Tazocin 5%](#) [Clarithromycin 14%](#) [Co-trimoxazole 65%](#) [Ciprofloxacin 11%](#) [Aciclovir 5%](#)

Co-trimoxazole is a combination of sulfamethoxazole and trimethoprim. These are bacteriostatic antibiotics that work by interfering with bacterial folate metabolism. However, they can also affect the host's folate metabolism. Methotrexate is a dihydrofolate reductase inhibitor. Therefore, together these medications can cause potentially life-threatening bone marrow suppression secondary to folate deficiency.

The BNF does not list interactions between corticosteroids and the remaining medication listed. Ciprofloxacin may possibly reduce methotrexate excretion, so monitoring for signs of potential toxicity needs to be undertaken. No interactions are listed in the BNF between methotrexate, and tazocin, aciclovir and clarithromycin.

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

### Indications

- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

### Adverse effects

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis

### Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

### Prescribing methotrexate

- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily

- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

#### Question 6 of 99

A 58-year-old man who has no fixed abode comes to the Emergency department because he is unable to walk. He has a history of alcoholism and type 2 diabetes. His main complaint is that his shoes have worn out and because of loss of sensation he didn't notice that he had stepped on a nail. In total the lesion on his right foot has been present for approximately 3 weeks.

Which of the following is the next step in evaluating his foot injury?

[Inflammatory markers5%](#) [MRI foot26%](#) [Plain x-ray foot60%](#) [USS foot4%](#) [Wound swab6%](#)

The key next step here is to gather useful information about the extent of any foot infection. By 3 weeks post injury, changes consistent with osteomyelitis should be visible on plain x-ray. These may include soft tissue swelling, bone demineralisation, cortical irregularity, and an elevated periosteum.

Many patients progress from a plain x-ray on to MRI imaging of the foot for further evaluation of the extent of infection and to guide potential operative approaches for debridement. Inflammatory markers are a very non-specific marker of infection and ultrasound of the foot is only useful to visualise soft tissue swelling or collection of pus / fluid. A wound swab is likely to show a range of bacteria, this is what drives selection of a broader spectrum antibiotic such as co-amoxiclav in the diabetic population.

### **Osteomyelitis**

Osteomyelitis describes an infection of the bone.

*Staph. aureus* is the most common cause except in patients with sickle-cell anaemia where

*Salmonella* species predominate.

#### Predisposing conditions

- diabetes mellitus
- sickle cell anaemia
- intravenous drug user
- immunosuppression due to either medication or HIV
- alcohol excess

#### Investigations

- MRI is the imaging modality of choice, with a sensitivity of 90-100%

#### Management

- flucloxacillin for 6 weeks
- clindamycin if penicillin-allergic

#### Question 7 of 99

This 60-year-old woman who is being treated for heartburn comes for review. She has developed some spots on her lips:





What is the most likely diagnosis?

[CREST syndrome](#)69% [Oesophageal cancer](#)3% [Vitamin C deficiency](#)5% [Peutz-Jeghers syndrome](#)18% [Iron-deficiency anaemia](#)4%

The heartburn may be explained by oesophageal dysmotility, a feature of CREST syndrome. The lesions on her lips are telangiectasia. She also has the typical tightening of the facial skin seen in patients with systemic sclerosis.

## Systemic sclerosis

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oesophageal dysmotility, Sclerodactyly, Telangiectasia

Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear



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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

## Question 8 of 99

A 32-year-old female with known rheumatoid arthritis presents to clinic and would like some advice. She would like to start a family with her partner. Her rheumatoid arthritis is current well-controlled on methotrexate and sulphasalazine, she has not required changing of doses for 2 years. She is reluctant to stop medications unless she has to, she had a number of flares when doses were reduced 3 years ago. What would you advise regarding her plans for pregnancy?

She should reconsider her plans for pregnancy. Stopping medications would make her disease uncontrollable and continuing medications will affect her child15% Continue sulphasalazine and methotrexate5% Stop sulphasalazine, continue methotrexate6% Continue sulphasalazine and stop methotrexate65% Stop both sulphasalazine and methotrexate9%

This is a relatively common scenario in rheumatology clinics: rheumatoid arthritis has a preponderance for females and a large number of RA patients are of child-bearing age<sup>1</sup>. The first



consideration is the need for treatment, then balancing the risks of disease flares and medical foetal toxicity. The majority of RA patients, as in most autoimmune disorders, experience improvements in their condition during pregnancy. Methotrexate is highly teratogenic and should be stopped between one and three months before pregnancy. Hydroxychloroquine and sulphasalazine are generally accepted to be DMARDs that can be continued during pregnancy. Sulphasalazine should, however, be avoided in male patients attempting conception due to the risks of oligospermia. Glucocorticoids cross the placenta in low doses and can be used after 14 weeks of pregnancy. Before this cut-off, there is an increased risk of cleft palate and gestational hypertension. Low doses of prednisolone is an option should flares occur when off methotrexate.

1. Dugowson CE, Koepsell TD, Voigt LF et al. Rheumatoid arthritis in women. Incidence rates in group health cooperative, Seattle, Washington, 1987-1989. *Arthritis Rheum.* 1991;34(12):1502

## **Rheumatoid arthritis: management**

The management of rheumatoid arthritis (RA) has been revolutionised by the introduction of disease-modifying therapies in the past decade. NICE has issued a number of technology appraisals on the newer agents and released general guidelines in 2009.

Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible. Other important treatment options include analgesia, physiotherapy and surgery.

### **Initial therapy**

- in the 2009 NICE guidelines it is recommend that patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)

### **DMARDs**

- methotrexate is the most widely used DMARD. Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- sulfasalazine
- leflunomide
- hydroxychloroquine

## TNF-inhibitors

- the current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- etanercept: recombinant human protein, acts as a decoy receptor for TNF- $\alpha$ , subcutaneous administration, can cause demyelination, risks include reactivation of tuberculosis
- infliximab: monoclonal antibody, binds to TNF- $\alpha$  and prevents it from binding with TNF receptors, intravenous administration, risks include reactivation of tuberculosis
- adalimumab: monoclonal antibody, subcutaneous administration

## Rituximab

- anti-CD20 monoclonal antibody, results in B-cell depletion
- two 1g intravenous infusions are given two weeks apart
- infusion reactions are common

## Abatacept

- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion
- not currently recommended by NICE

## Question 9 of 99

An 85-year-old woman presents with a long history of poorly controlled type 2 diabetes mellitus presents to her GP complaining of a swollen right foot. She describes it as a 'gammy' foot and says she is always tripping over it. The pain is described as being 2 out of 10. The patient also describes reduced sensation up to her ankles.

On examination she has reduced sensation in both feet. The right midfoot is swollen, warm and slightly erythematous but there is no ulcer present. The dorsalis pedis pulse is difficult to feel on the right hand side.

An x-ray is requested:



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What is the most likely diagnosis?

[Septic arthritis of the 1st metatarsophalangeal joint4% Osteomyelitis12% Charcot joint72% Critical ischaemia of the right foot secondary to peripheral arterial disease6% Gout6%](#)

The x-ray shows extensive bone remodeling / fragmentation involving the midfoot. In combination with the presence of a swollen, red, warm joint in a patient with a history of poorly controlled diabetes is highly suggestive of a Charcot's joint.

The x-ray findings are not consistent with osteomyelitis and questions would often give other clues such as an overlying ulcer, which is not present in this case.

## **Charcot joint**

A Charcot joint is also commonly referred to as a neuropathic joint. It describes a joint which has become badly disrupted and damaged secondary to a loss of sensation. In years gone by they were most commonly caused by neuropathy secondary to syphilis (tabes dorsalis) but are now most commonly seen in diabetics.

### **Features**

- Charcot joints are typically a lot less painful than would be expected given the degree of joint disruption due to the sensory neuropathy. However, 75% of patients report some degree of pain
- the joint is typically swollen, red and warm



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Extensive bone remodeling / fragmentation involving the midfoot in this patient with a poorly controlled diabetes, compatible with Charcot's joint (neuropathic arthropathy)

uestion 10 of 99

A 30-year-old woman with systemic lupus erythematosus is seen in the rheumatology clinic for annual follow-up. Recently she has felt well in herself and continues on hydroxychloroquine. She has not required additional steroid or analgesia for the last three years.

Her routine blood tests are as follows:

Hb	112 g/l	Na <sup>+</sup>	136 mmol/l
Platelets	252 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.9 mmol/l
WBC	6 * 10 <sup>9</sup> /l	Urea	15 mmol/l
Neuts	4.5 * 10 <sup>9</sup> /l	Creatinine	180 µmol/l
Lymphs	1 * 10 <sup>9</sup> /l	CRP	23 mg/l

Her urine dipstick shows 3+ blood and 2+ protein.

Given that her renal function was previously normal, her rheumatologist refers her for ultrasound kidneys which shows normal sized kidneys with no hydronephrosis and normal renal artery dopplers.

Following discussion at MDT, it is recommended she undergo kidney biopsy for suspected lupus nephritis.

Which class of lupus nephritis would carry the worst prognosis?

[Focal7%Diffuse47%Minimal mesangial3%Mesangial proliferative29%Membranous14%](#)

Lupus nephritis is split into 5 classes, of which class IV, diffuse proliferative, carries the worst mortality and renal outcome.

Reference: Faurschou M et al. Long term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res. 2010;62;873-880.

## **Systemic lupus erythematosus: features**

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder. It typically presents in early adulthood and is more common in women and people of Afro-Caribbean origin.

General features

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

## Skin

- malar (butterfly) rash: spares nasolabial folds
- discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- photosensitivity
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

## Musculoskeletal

- arthralgia
- non-erosive arthritis

## Cardiovascular

- myocarditis

## Respiratory

- pleurisy
- fibrosing alveolitis

## Renal

- proteinuria
- glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type)

## Neuropsychiatric

- anxiety and depression
- psychosis
- seizures

### Question 1 of 89

A 46-year-old lady complains of proximal muscle weakness over 6 months. History is otherwise unremarkable. She has no past medical history and is on no medications. She does not drink alcohol. On examination, power is 4/5 proximally in both arms and legs, otherwise unremarkable. Blood investigations are normal except for an elevated creatinine kinase level at 900 U/L. Electromyography demonstrates myopathic features. You order a muscle biopsy to help differentiate which myopathy is present. The results show endomysial lymphocytic infiltrates that invade nonnecrotic muscle fibres. What is the most likely diagnosis?

[Dermatomyositis8%](#) [Inclusion body myositis33%](#) [Systemic lupus erythematosus3%](#) [Lung cancer3%](#) [Polymyositis52%](#)

Proximal muscle weakness is a nonspecific complaint and the elevated CK with this presentation suggests a myopathy, of which the common are inflammatory (polymyositis, dermatomyositis, and inclusion body myositis), toxic myopathies (e.g. statin- or alcohol-induced), and inherited (Duchenne/Becker muscular dystrophy, myotonic dystrophy). There is no history of toxic agents here and the history is not lifelong to suggest an inherited causes. There are no skin changes to suggest dermatomyositis. The diagnostic difficulty may be between inclusion body myositis and polymyositis. The former tends to affect wrists and fingers more than the latter. Where there is diagnostic difficulty clinically, a biopsy may help make a diagnosis:

Endomysial lymphocytic infiltrates that invade nonnecrotic muscle fibres = polymyositis

Perimysial inflammation of lymphocytes and parafascicular atrophy = dermatomyositis

Inflammatory infiltrates and inclusions within muscle fibres = inclusion body myositis.

Polymyositis responds to immunosuppression.

It is likely she has a polymyositis and coincidental carpal tunnel syndrome rather than an inclusion body myositis.

## Polymyositis

### Overview

- inflammatory disorder causing symmetrical, proximal muscle weakness



- thought to be a T-cell-mediated cytotoxic process directed against muscle fibres
- may be idiopathic or associated with connective tissue disorders
- associated with malignancy
- dermatomyositis is a variant of the disease where skin manifestations are prominent, for example a purple (heliotrope) rash on the cheeks and eyelids
- typically affects middle-aged, female: male 3:1

## Features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

## Investigations

- elevated creatine kinase
- EMG
- muscle biopsy
- anti-Jo-1 antibodies are seen in pattern of disease associated with lung involvement, Raynaud's and fever

## Question 2 of 89

A 79-year-old woman falls over on to an outstretched hand and sustains a Colles' fracture (fracture of the distal radius). She has no past medical history of note other than depression and osteoarthritis. What is the most appropriate next course of action with regards to her risk of sustaining a further fracture?

[Arrange a DEXA scan](#)25% [Perform a FRAX \(without bone mineral density\) assessment](#)15% [Start alendronate 70mg once weekly](#)50% [No further action is required](#)6% [Arrange a myeloma screen](#)4%

Start alendronate in patients  $\geq 75$  years following a fragility fracture, without waiting for a DEXA scan

Given her age she is presumed to have osteoporosis and therefore started on oral alendronate 70mg once weekly. A DEXA scan does not need to be arranged.

## **Osteoporosis: Assessing patients following a fragility fracture**

The management of patients following a fragility fracture depends on age.

### **Patients $\geq$ 75 years of age**

Patients who've had a fragility fracture and are  $\geq$  75 years of age are presumed to have underlying osteoporosis and should be started on first-line therapy (an oral bisphosphonate), without the need for a DEXA scan.

It should be noted that the 2014 NOGG guidelines have a different threshold, suggesting treatment is started in all women over the age of 50 years who've had a fragility fracture - *'although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.'*

### **Patients $<$ 75 years of age**

If a patient is under the age of 75 years a DEXA scan should be arranged. These results can then be entered into a FRAX assessment (along with the fact that they've had a fracture) to determine the patients ongoing fracture risk.

For example, a 79-year-old woman falls over on to an outstretched hand and sustains a Colles' fracture (fracture of the distal radius). Given her age she is presumed to have osteoporosis and therefore started on oral alendronate 70mg once weekly. No DEXA scan is arranged.

### **Question 3 of 89**

A 60-year-old man presents with a few hours history of severe left sided headache, described as a sharp pain behind the eye and around the temple. When his scalp is touched it elicits severe pain. He describes a transient loss of vision in the left eye that lasted for seconds during the onset of the pain. He has been feeling unwell with fevers and intermittent headaches for the past week. 2 years ago he had been diagnosed with cluster headaches and has had them intermittently, the last attack was 3 months ago.

On examination his scalp was tender to touch, and a prominent temporal artery could be felt. The temperature was 37.9°C, heart rate 90bpm, respiratory rate 22 breaths per minute, saturating 100% on air. Pupils were equal and reactive to light, no photophobia. no diplopia or ophthalmoplegia on eye movements. Rest of cranial nerve examination was normal. Fundoscopy revealed no evidence of papilloedema.

Na+	137mmol/l
K+	4.3 mmol/l
Urea	5.7 mmol/l
Creatinine	67 µmol/l
Serum glucose	5.8 mmol/l
C Reactive protein (CRP)	78mg/l
Erythrocyte Sedimentation Rate (ESR)	Awaiting results.
Haemoglobin	156 g/l
White cell count	10.2 x 10 <sup>9</sup> /L
INR	1.0

What is the next appropriate management step?

CT Head scan 5% Intravenous normal saline 4% 15L oxygen via a non re-breather mask  
6% Prednisolone 60mg orally 80% 200mg Ibuprofen 4%

This patient has presented with symptoms and signs suggestive of temporal arteritis. Temporal arteritis is a systemic immune-mediated vasculitis affecting medium and large-sized arteries. It typically presents with temporal headache, myalgia, malaise or fever. Symptoms can be subtle. Other features include jaw claudication, diplopia. On examination, there may be scalp tenderness, prominent, beaded or tender temporal arteritis, fever and bruits heard over the carotid, axillary arteries may be present. The history of cluster headaches is a red herring.

CRP can be elevated, even in the presence of a normal ESR. A normal ESR does not exclude the diagnosis. Therefore in this case the next most appropriate management step would be to give high dose steroids (40mg prednisolone, unless the patient has ischaemic, claudication or visual symptoms - give 60mg prednisolone daily instead). Low dose aspirin 75mg daily should be started unless there are contra indications.

A CT scan is not indicated at this point. Oxygen is used in the treatment of cluster headaches.

## **Temporal arteritis**

Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%)
- visual disturbances secondary to anterior ischemic optic neuropathy
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also lethargy, depression, low-grade fever, anorexia, night sweats

### Investigations

- raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- temporal artery biopsy: skip lesions may be present
- note creatine kinase and EMG normal

### Treatment

- high-dose prednisolone - there should be a dramatic response, if not the diagnosis should be reconsidered
- urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible

### Question 4 of 89

A 52-year-old lady was seen in the general medicine clinic with aches and pains. The pains were present in her arms and legs, and not associated with her joints. They have been present for several months, and she was unable to identify any precipitating factors. She also felt that on occasion she felt generally weak and tired, though denied the presence of any specific weakness. Her past medical history comprised of epilepsy which was well controlled with phenytoin 500mg BD for several years, as well as hypertension and asthma. In addition to phenytoin 500mg BD she was prescribed ramipril 5mg OD, Clenil modulite 200mcg BD, salmeterol 100mcg BD and Elleste duo for the last six months. Upon specific questioning, she stated that she ate a nutritionally balanced diet, and that she had not suffered a previous fracture. Her mother was diagnosed with osteoporosis when she was 64-years-old, and she did not smoke. She drank 10 units of alcohol per week.

On examination, she was systemically well, with a blood pressure of 132/68 mmHg, heart rate 84, respiratory rate 16/min and body mass index of 23. Examination of her cardiovascular system revealed the presence of normal heart sounds and was unremarkable. Examination of the

respiratory and gastrointestinal systems was likewise unremarkable except for the presence of gingival hypertrophy. Examination of the musculoskeletal system revealed the presence of Heberden's nodes but was also otherwise unremarkable with a full range of movement in all joints. Examination of the neurological system was normal with a power of 5/5 in all muscle groups and normal sensation, tone and coordination. Cranial nerve and fundoscopy examinations were unremarkable. Examination of the thyroid gland was unremarkable.

Investigations revealed the following results:

Bilirubin	22 µmol/l
ALP	262 u/l
ALT	23 u/l
Albumin	42 g/l
Protein	76 g/l
Globulin	34 g/l
Adjusted calcium	2.06 mmol/l
Phosphate	0.78 mmol/l
Vitamin D level	pending result
Parathyroid hormone	88 (NR 11-54 pg/ml)
IgG	11.2 g/L (NR 7.0 18.0)
IgA	3.2 g/L (NR 0.8 4.0)
IgM	2.1 g/L (NR 0.4 2.5)

Urinary Bence Jones Protein: negative

What is the most likely underlying diagnosis?

[Fibromyalgia9%](#)[Paget's disease 14%](#)[Primary hyperparathyroidism15%](#)[Osteoporosis6%](#)[Osteomalacia55%](#)

Phenytoin is known to affect the metabolism of vitamin D, and over prolonged periods of time may result in osteomalacia. This patient is also likely suffering other sequelae of prolonged phenytoin use as manifested by the presence of gingival hypertrophy. She has a raised parathyroid hormone level secondary to the low vitamin D level, and there is no evidence of osteoporosis.

## **Osteomalacia**

Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion

### Types

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- renal failure
- drug induced e.g. anticonvulsants
- vitamin D resistant; inherited
- liver disease, e.g. cirrhosis

### Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

### Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase
- x-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (Looser's zones or pseudofractures)

### Treatment

- calcium with vitamin D tablets

### Question 5 of 89

The radiograph below was taken from a patient who presented with pain, swelling and erythema of the right knee.



© Image used on license from [Radiopaedia](#)



What is the diagnosis?

[Osteoarthritis23%](#)[Rheumatoid arthritis7%](#)[Pseudogout52%](#)[Gout10%](#)[Tibial plateau fracture8%](#)

The radiograph demonstrates chondrocalcinosis (visible calcification of cartilage), a sign pathognomonic of pseudogout.

## **Pseudogout**

Pseudogout is a form of microcrystal synovitis caused by the deposition of calcium pyrophosphate dihydrate in the synovium

Risk factors

- hyperparathyroidism
- hypothyroidism
- haemochromatosis

- acromegaly
- low magnesium, low phosphate
- Wilson's disease

## Features

- knee, wrist and shoulders most commonly affected
- joint aspiration: weakly-positively birefringent rhomboid shaped crystals
- x-ray: chondrocalcinosis

## Management

- aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

## Question 6 of 89

A 50-year-old patient comes in with a six-month history of polyarthralgia in her hands. Blood tests show she is rheumatoid factor positive, anti-CCP antibody positive and anti nuclear antibody positive with a high titre. An ultrasound scan confirms active synovitis in the metacarpophalangeal joints of her hands bilaterally. What drug regime would you start this lady on?

[Methotrexate and prednisolone21%](#) [Methotrexate and hydroxychloroquine7%](#) [Sulfasalazine and hydroxychloroquine4%](#) [Sulfasalazine, hydroxychloroquine and prednisolone7%](#) [Methotrexate, hydroxychloroquine and prednisolone61%](#)

This patient has seropositive rheumatoid arthritis. According to the British Society of Rheumatology, she should be started on dual disease modifying therapy. These take several months to reach maximal effect so it is important to cover the patient with steroids to give them symptomatic relief in the early stages of treatment.

Given this lady is anti-nuclear antibody (ANA) positive with a high titre she is at a much greater risk of side effects with sulfasalazine. Often this manifests itself with a Stevens-Johnson type reaction featuring a rash, oral ulceration and systemic symptoms. Therefore, in this case, methotrexate and hydroxychloroquine would be the disease modifying antirheumatic drug (DMARD) combination of choice.

Full guidelines are here:



<http://rheumatology.org.uk/includes/documents/cmdocs/2009/m/managementofrheumatoidarthritisfirst2years.pdf>

## **Rheumatoid arthritis: management**

The management of rheumatoid arthritis (RA) has been revolutionised by the introduction of disease-modifying therapies in the past decade. NICE has issued a number of technology appraisals on the newer agents and released general guidelines in 2009.

Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible. Other important treatment options include analgesia, physiotherapy and surgery.

### **Initial therapy**

- in the 2009 NICE guidelines it is recommended that patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)

### **DMARDs**

- methotrexate is the most widely used DMARD. Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- sulfasalazine
- leflunomide
- hydroxychloroquine

### **TNF-inhibitors**

- the current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- etanercept: recombinant human protein, acts as a decoy receptor for TNF- $\alpha$ , subcutaneous administration, can cause demyelination, risks include reactivation of tuberculosis
- infliximab: monoclonal antibody, binds to TNF- $\alpha$  and prevents it from binding with TNF receptors, intravenous administration, risks include reactivation of tuberculosis
- adalimumab: monoclonal antibody, subcutaneous administration

## Rituximab

- anti-CD20 monoclonal antibody, results in B-cell depletion
- two 1g intravenous infusions are given two weeks apart
- infusion reactions are common

## Abatacept

- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion
- not currently recommended by NICE

## Question 7 of 89

A 25-year-old woman with rheumatoid arthritis has returned to clinic complaining of a loss of taste sensation. Over the last few months, her early morning stiffness has been causing more problems and she also has been troubled by pain in both knees even after taking paracetamol and naproxen.

She was last reviewed one month ago and since then her joint stiffness and pain has improved slightly. On examination, there is a good range of movement in the knees. Her mucous membranes are moist and there are no ulcers in the mouth. Which of the following is most likely responsible?

[Anaemia of chronic disease5%](#)[Recent dose increase of hydroxychloroquine32%](#)[Associated Sjogren's syndrome17%](#)[Addition of penicillamine to her regimen41%](#)[Chronic use of tramadol to control her joint pain5%](#)

A known side effect of penicillamine is a loss of taste sensation. Sjogren's may well present in association with rheumatoid arthritis but is more likely to cause a dry mouth than a loss of taste.

## Penicillamine

### Mechanism of action

- largely unknown
- thought to reduce IL-1 synthesis and prevent the maturation of newly synthesized collagen

#### Uses

- rheumatoid arthritis

#### Adverse effects

- rashes
- disturbance of taste
- proteinuria

#### Question 1 of 82

A 45-year-old patient comes in with a polyarthralgia. She is getting cyclical fevers along with the pain and also mentions she gets a salmon pink rash on her torso. She says she has had flares of this in the past and previously has been admitted to ITU for intravenous medications but she cannot recall their names. Her flares started in her late twenties. She has not had a flare for many years now. Her regular medications consist of paracetamol 1g PRN and naproxen 500mg PRN. On examination, she is tender in most of her joints including her hips, knees, wrists, shoulders and the small joints of her hands. Her observations show a heart rate of 110/min, respiratory rate of 24/min, blood pressure of 96/65mmHg, oxygen saturations of 98% on room air and temperature 39°C. Her blood tests reveal:

Hb	135 g/l	Na <sup>+</sup>	136 mmol/l
Platelets	269 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.6 mmol/l
WBC	8 * 10 <sup>9</sup> /l	Urea	5 mmol/l
Neuts	6 * 10 <sup>9</sup> /l	Creatinine	90 µmol/l
Lymphs	2 * 10 <sup>9</sup> /l	CRP	55 mg/l
Eosin	0.1 * 10 <sup>9</sup> /l	Ferritin	1559 ng/ml

What is the most likely diagnosis?

[Adult-onset Still's disease87%](#)[Rheumatoid arthritis3%](#)[Septic arthritis3%](#)[Psoriatic arthritis4%](#)[Tuberculosis3%](#)

This patient is suffering from adult-onset Still's disease shown by the triad of fever, polyarthralgia and rash. The raised ferritin is another hint at the diagnosis as ferritin is the acute

phase protein of choice for monitoring disease activity in these patients. Adult-onset Still's disease can lead to severe flares that mimic sepsis.

A range of biologic therapies can be used to treat these flares such as anti-TNFs and anakinra along with more traditional disease modifying anti rheumatic drugs (DMARDs) and non-steroidal anti inflammatories.

Rheumatoid arthritis would be a differential but the triad listed is more associated with Still's disease. In this case, it is adult onset Still's as it started in her twenties. Septic arthritis tends to be monoarthritis or occasionally an oligoarthritis, not a polyarthritis, hence this is not the correct answer. The rash described is not that psoriasis.

### **Still's disease in adults**

#### Adult Still's disease

- typically affects 16-35 year olds

#### Features

- arthralgia
- elevated serum ferritin
- rash: salmon-pink, maculopapular
- pyrexia
- lymphadenopathy
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

#### Question 2 of 82

A 35-year-old woman presents with alopecia. For the past few months she has noticed some 'scaly' patches on her scalp. Once healed they normally leave a scar and no hair seems to grow back. Her scalp has the following appearance:



© Image used on license from [DermNet NZ](#)



What is the most likely diagnosis?

[Discoid lupus erythematosus](#)61% [Alopecia areata](#)18% [Psoriasis](#)10% [Trichotillomania](#)7% [Squamous cell carcinoma](#)4%

Remember that alopecia may be divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle):

Scarring alopecia

- trauma, burns
- radiotherapy
- lichen planus
- discoid lupus
- tinea capitis (if untreated)

Non-scarring alopecia

- male-pattern baldness
- drugs: cytotoxic drugs, carbimazole, heparin, oral contraceptive pill, colchicine
- nutritional: iron and zinc deficiency
- autoimmune: alopecia areata
- telogen effluvium (hair loss following stressful period e.g. surgery)
- trichotillomania

Even if you are not familiar with the appearance of discoid lupus erythematosus (along with most non-dermatologists) this leaves it as the only possible answer.

### **Discoid lupus erythematosus**

Discoid lupus erythematosus is a benign disorder generally seen in younger females. It very rarely progresses to systemic lupus erythematosus (in less than 5% of cases). Discoid lupus erythematosus is characterised by follicular keratin plugs and is thought to be autoimmune in aetiology

#### Features

- erythematous, raised rash, sometimes scaly
- may be photosensitive
- more common on face, neck, ears and scalp
- lesions heal with atrophy, scarring (may cause scarring alopecia), and pigmentation

#### Management

- topical steroid cream
- oral antimalarials may be used second-line e.g. hydroxychloroquine
- avoid sun exposure



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Discoid lupus erythematosus affecting the scalp

### Question 3 of 82

A 34-year-old woman is reviewed in clinic. She has been suffering from increasing tiredness for the last three months. She has no other symptoms and specifically denies pain, bleeding, weight loss and mood problems. She has a past medical history of asthma but has not needed her blue inhaler in over a year. She has no allergies. Her only regular medication is the oral contraceptive pill. Blood tests show a normal FBC, U&Es, calcium, parathyroid hormone but low vitamin D (32 nmol/L). What is the most appropriate treatment in regards to her low vitamin D?

[Dietary advise only10%](#)[Loading dose vitamin D28%](#)[Maintenance dose vitamin D44%](#)[Combined calcium and vitamin D11%](#)[No treatment needed6%](#)

This patient has vitamin D insufficiency which may explain her tiredness. This should be managed with maintenance dose vitamin D. Loading dose would be appropriate if her serum level was less than 30 nmol/L. Dietary advice would be appropriate for patients with adequate levels, above 50 nmol/L. As calcium is normal and there is no evidence of low calcium diet there is no need for calcium supplementation.

Vitamin D deficiency versus insufficiency

Description	Serum levels	Treatment
Adequate vitamin D	>50 nmol/L	dietary recommendations

<b>Description</b>	<b>Serum levels</b>	<b>Treatment</b>
Insufficient vitamin D	30-50 nmol/L	maintenance dose vitamin D
Deficient vitamin D	<30 nmol/L	loading dose vitamin D

Source:

'Vitamin D Deficiency in Adults - Treatment and Prevention.' Clinical Knowledge Summaries. National Institute for Health and Care Excellence, Nov. 2016.

## **Osteomalacia**

### Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion

### Types

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- renal failure
- drug induced e.g. anticonvulsants
- vitamin D resistant; inherited
- liver disease, e.g. cirrhosis

### Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

### Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase
- x-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (Looser's zones or pseudofractures)



## Treatment

- calcium with vitamin D tablets

### Question 1 of 79

A 55-year-old woman presents for review. Her mother has just been discharged after suffering a hip fracture. She is concerned that she may have 'inherited' osteoporosis and is asking what she should do. She has no significant past medical history of note, takes no regular medication and has never sustained any fractures. She smokes around 20 cigarettes per day and drinks about 3-4 units of alcohol per day.

What is the most appropriate course of action?

[Arrange bone mineral density measurement \(DEXA scan\)28%](#)[Reassure her that assessment of fragility fracture risk does not need to be done until 65 years12%](#)[Refer her to the genetics team for a risk assessment3%](#)[Start first-line bone protection \(i.e. ensure calcium/vitamin D replete + oral bisphosphonate\)6%](#)[Use the FRAX tool51%](#)

This lady has a number of risk factors for developing osteoporosis:

- positive family history
- smoking
- excess alcohol intake

She should therefore have an immediate FRAX assessment, rather than waiting until 65 years as we would for women without any relevant risk factors

## Osteoporosis: assessing risk

We worry about osteoporosis because of the increased risk of fragility fractures. So how do we assess which patients are at risk and need further investigation?

NICE produced guidelines in 2012: Osteoporosis: assessing the risk of fragility fracture. The following is based on those guidelines.

They advise that all women aged  $\geq 65$  years and all men aged  $\geq 75$  years should be assessed. Younger patients should be assessed in the presence of risk factors, such as:

- previous fragility fracture
- current use or frequent recent use of oral or systemic glucocorticoid
- history of falls
- family history of hip fracture
- other causes of secondary osteoporosis
- low body mass index (BMI) (less than 18.5 kg/m<sup>2</sup>)
- smoking
- alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

## Methods of risk assessment

NICE recommend using a clinical prediction tool such as FRAX or QFracture to assess a patient's 10 year risk of developing a fracture. This is analogous to the cardiovascular risk tools such as QRISK.

### FRAX

- estimates the 10-year risk of fragility fracture
- valid for patients aged 40-90 years
- based on international data so use not limited to UK patients
- assesses the following factors: age, sex, weight, height, previous fracture, parental fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol intake
- bone mineral density (BMD) is optional, but clearly improves the accuracy of the results. NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result

### QFracture

- estimates the 10-year risk of fragility fracture
- developed in 2009 based on UK primary care dataset
- can be used for patients aged 30-99 years (this is stated on the QFracture website, but other sources give a figure of 30-85 years)
- includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants

There are some situations where NICE recommend arranging BMD assessment (i.e. a DEXA scan) rather than using one of the clinical prediction tools:

- before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).

- in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).

## Interpreting the results of FRAX

Once we've decided that we need to do a risk assessment using FRAX and have entered all the data we are left with results to interpret.

If the FRAX assessment was done **without a bone mineral density (BMD)** measurement the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:

- low risk: reassure and give lifestyle advice
- intermediate risk: offer BMD test
- high risk: offer bone protection treatment

Therefore, with intermediate risk results FRAX will recommend that you arrange a BMD test to enable you to more accurately determine whether the patient needs treatment

If the FRAX assessment was done **with a bone mineral density (BMD)** measurement the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:

- reassure
- consider treatment
- strongly recommend treatment

If you use QFracture instead patients are not automatically categorised into low, intermediate or high risk. Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture. This data then needs to be interpreted alongside either local or national guidelines, taking into account certain factors such as the patient's age.

## When should we reassess a patient's risk?

NICE recommend that we recalculate a patient's risk (i.e. repeat the FRAX/QFracture):

- *if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, or*
- *when there has been a change in the person's risk factors*

Question 2 of 79

An 80-year-old man presents is taken to the Emergency Department after falling at home. His daughter notes that he fell onto his left side. An x-ray is taken of the pelvis:



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What is the diagnosis?

[Paget's disease of the bone](#)28%[Severe osteoarthritis](#)40%[Left intertrochanteric fracture](#)12%[Left subcapital fracture](#)17%[Myeloma](#)4%

This x-ray shows advanced osteoarthritic changes at the left hip joint; loss of joint space and subchondral sclerosis are prominent.

### **Osteoarthritis: x-ray changes**

X-ray changes of osteoarthritis

- decrease of joint space
- subchondral sclerosis
- subchondral cysts
- osteophytes forming at joint margins

### Question 3 of 79

You are the medical doctor on an acute medical admissions unit. A 56-year old female with hypertension, pulmonary fibrosis and a recent diagnosis of Raynaud's phenomenon presents with generally feeling unwell. On further questioning she also reports dysphagia for the past few months for which she is awaiting investigations under the gastroenterology team at your hospital. She is currently only on amlodipine 5mg od.

Her observations are: temperature 36.4°C, pulse 88/min, blood pressure 172/88 mmHg, respiratory rate 14/min, sats 100% on room air. Her chest is clear and abdomen soft, non-tender. Blood tests reveal an acute kidney injury with: sodium 141 mmol/l, potassium 4.6 mmol/l, urea 27 mmol/l, creatinine 320 µmol/l (her GP notes state she had a normal renal function from a routine blood test 1 month ago).

What is the most appropriate treatment at this stage?

[Fluids19%Stat 5mg amlodipine6%Stat angiotensin-converting enzyme inhibitor \(ACE-i\)63%Haemodialysis7%Haemofiltration6%](#)

This lady has features of diffuse cutaneous systemic sclerosis - she has Raynaud's phenomenon, pulmonary fibrosis and dysphagia. Her current presentation is that of scleroderma renal crisis. This is a medical emergency and treatment should be administered as soon as possible. The most appropriate treatment initially would be an ACE-i with a consideration for dialysis and renal transplantation if required.

### Systemic sclerosis

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

### Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

### Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

### Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear



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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

Question 4 of 79

A 73-year-old woman attends your clinic with the results of her DEXA scan:

Left neck of femur -2.8

Right neck of femur -3.0

Her medical history is notable for previous pulmonary embolism and hyperparathyroidism.

You discuss bone protection, but she developed a severe rash to her bisphosphonates and is not willing to restart any drug of that class.

Which of these describes the mechanism of action of the next most appropriate therapy?

[Selective oestrogen receptor modulator \(SERM\)20%](#)[Recombinant parathyroid hormone9%](#)[Incorporation into bone in place of calcium6%](#)[RANKL inhibitor58%](#)[Farnesyl diphosphate synthase \(FPPS\) inhibitor8%](#)

Denosumab - RANKL inhibitor

This woman has critical osteoporosis and is susceptible to a fragility fracture. Many patients have reactions to bisphosphonates and being aware of the contraindications for the numerous other medications is important.

Raloxifene is a SERM and is contraindicated in previous thromboembolic disease. Strontium is also contraindicated in previous venous thromboembolism and works by being incorporated into bone in place of calcium (due to its atomic similarities).

Teriparatide is a recombinant form of parathyroid hormone and is contraindicated in previous hyperparathyroidism.

FPPS inhibition is the mechanism by which bisphosphonates have their effect.

As such, denosumab is the most appropriate next step. It is a RANKL inhibitor and requires 6 monthly subcutaneous injections. It is recommended by NICE for patients who are unable to tolerate or are precluded from the other options.

## **Denosumab**

Denosumab is a relatively new treatment for osteoporosis. It is a human monoclonal antibody



that inhibits osteoclast formation, function and survival. Remember that osteoblasts build bone, osteoclasts eat bone. It is given as a subcutaneous injection, at a dose of 60mg, every 6 months.

A larger dose of denosumab (120mg) may also be given every 4 weeks for the prevention of skeletal-related events (i.e. pathological fractures) in adults with bone metastases from solid tumours. For example, you may have noticed some of your breast cancer patients have been prescribed denosumab.

### **Where does it fit in the management of osteoporosis?**

Oral bisphosphonates are still given first-line, with oral alendronate being the first-line treatment. If alendronate is not tolerated then NICE recommend using an alternative bisphosphonate - either risedronate or etidronate. Following this the advice becomes more complicated with the next-line medications only being started if certain T score and other risk factor criteria being met. Raloxifene and strontium ranelate were recommended as next-line drugs in the NICE criteria but following recent safety concerns regarding strontium ranelate it is likely there will be an increasing role for denosumab.

NICE published a technology appraisal looking at the role of denosumab in 2010. A link is provided.

### **What are the known side-effects of denosumab?**

Denosumab is generally well tolerated. Dyspnoea and diarrhoea are generally considered the two most common side effects, occurring in around 1 in 10 patients. Other less common side effects include hypocalcaemia and upper respiratory tract infections.

### **What does the Drug Safety Update add?**

Cases of atypical femoral fractures have been noted in patients taking denosumab. Doctors are advised to look out for patients complaining of unusual thigh, hip or groin pain.

### **Question 5 of 79**

A 60-year-old man, recently diagnosed to have seropositive rheumatoid arthritis presented with progressive shortness of breath and dry cough for the past 3 weeks. He was started on methotrexate at a dose of 10 mg per week, 2 months back by his treating physician.

On examination, his pulse rate was 120/min, respiratory rate was 24/min, blood pressure was 130/80 mmHg. His SpO<sub>2</sub> in room air was 88%. Auscultation of the chest showed bilateral basal crackles.

A CT chest was taken which showed bilateral diffuse ground glass changes with peripheral reticular lines and few patchy consolidative changes. The treating respiratory physician made a provisional diagnosis of methotrexate induced lung injury.

What would you suggest to prevent further lung damage?

[Folic acid supplementation18%Oxygen supplementation5%Switching from weekly to lower dose daily administration of methotrexate7%Decreasing the dose of methotrexate28%Prednisolone42%](#)

Supplemental folic acid which selectively rescues normal cells from methotrexate toxicity does not reduce the risk for methotrexate induced lung injury suggesting alternate mechanisms for lung injury other than depleting intracellular folate reserves. Oxygen can be supplemented to correct hypoxaemia but is not found to prevent further lung damage. Relapse is common with methotrexate re-challenge and hence re-introduction of methotrexate should be avoided as much as possible either as daily or weekly dose. Steroids owing to their anti-inflammatory properties are indicated with severe pulmonary toxicity to prevent further lung damage.

Reference: 1) Fishman's pulmonary diseases and disorders-4th edition

2) Pilar Barrera, Roland F J M Laan, Piet L C M van Riel, P N Richard Dekhuijzen, Agnes M Th Boerbooms, Levinus B A van de Putte, Annals of the Rheumatic diseases 1994;53;434-439

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

### **Indications**

- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

### **Adverse effects**

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis

- liver cirrhosis

### Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

### Prescribing methotrexate

- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

### Question 1 of 74

A 30-year-old lady with rheumatoid arthritis, presents feeling unwell. She has felt lethargic for the last two days and over the last 24 hours has developed a severe sore throat. She has been on the following prescription for the last six months; paracetamol 1g QDS, naproxen 500mg PRN, methotrexate 15mg once weekly, folic acid 5mg once weekly and prednisolone 5mg OD. She is septic on examination with observations as follows: respiratory rate 26/min, heart rate 120/min, blood pressure 100/67mmHg, temperature 37.9°C. She is tolerating oral fluids and small amounts of food. Adequate fluid resuscitation and antibiotics are started. With regards to her regular medications what should be done?

[Hold methotrexate and half dose of prednisolone](#)8%[Hold methotrexate and increase prednisolone to 10mg once daily](#)57%[Half dose of methotrexate and increase prednisolone to 10mg once daily](#)9%[Refer to rheumatology for urgent review](#)9%[Hold methotrexate and start IV methylprednisolone](#)16%

This lady should be presumed to be septic, she has been started on the relevant antibiotics and

fluids as it states in the question. She needs her immunosuppression held and therefore no methotrexate should be given. Given that she is on long term steroids these need to be doubled to make sure she does not become Addisonian.

A referral to rheumatology would be appropriate following adequate resuscitation and treatment of the patient. Currently, her rheumatoid arthritis is not the priority.

## **Methotrexate**

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- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

#### Question 2 of 74

A 60 year old woman attended her General Practitioner and reported a three month history of bilateral shoulder muscle and bilateral hip girdle aches and pain. She also experienced stiffness affecting these areas that lasted for up to two hours each morning. These symptoms were limiting her day to day activities and were unresponsive to simple analgesics.

The patient denied symptoms of headache, visual disturbance or jaw claudication. Intermittent episodes of dry mouth and dry eyes had been present for several years. There was no history of unexplained skin rashes. Past medical history included coeliac disease diagnosed twenty years previously that was well controlled on a gluten-free diet. The patient was a non-smoker and drank alcohol only occasionally.

Examination revealed mild muscular tenderness across the shoulder and hip girdles although with no other inflamed or tender joints. Cardiovascular and respiratory examination was unremarkable.

Blood tests requested by her GP demonstrated an elevated ESR of 65. A diagnosis of PMR was made and a course of 20 mg prednisolone daily prescribed. However 6 weeks later the patients symptoms had not significantly improved and she was referred to rheumatology clinic. Repeat blood tests and other investigations are listed below.

Haemoglobin	110 g / dL
White cell count	$8.9 \times 10^9/l$
Neutrophils	$7.8 \times 10^9/l$
Platelets	$456 \times 10^9/l$
Urea	6.2 mmol / L
Creatinine	87 micromol / L
Sodium	138 mmol / L

Potassium	4.1 mmol / L
Ferritin	180 ng / mL
Erythrocyte sedimentation rate	75 mm / h
Rheumatoid factor	Negative
Connective tissue ANA	Negative
Anti-CCP antibodies	58 EU (reference < 20)
Creatinine kinase	89 U / L (reference 5-130)

X-ray hands: minor degenerative change in multiple inter-phalangeal joints of both hands; no evidence of erosive arthropathy

What is correct diagnosis?

[Polymyalgia rheumatica 13%](#) [Rheumatoid arthritis 54%](#) [Polymyositis 9%](#) [Sjorgren's syndrome 18%](#) [Systemic lupus erythematosus 6%](#)

Rheumatoid arthritis can present with a polymyalgic syndrome prior to clinically detectable synovitis. In this case this is suggested by the lack of response to trial of prednisolone and the positive anti-CCP antibody. Observational studies have shown a greater clinical and laboratory response to steroids in polymyalgia rheumatica than polymyalgic onset rheumatoid arthritis. Anti-CCP antibodies are rarely present in polymyalgia rheumatica but are strongly associated with rheumatoid arthritis.

Sjorgren's syndrome and SLE are unlikely given the lack of anti-nuclear antibodies. Polymyositis is excluded by the normal CK.

Mackie S, Mallen C. Polymyalgia rheumatica. BMJ 2013;347:f6937.

## **Rheumatoid arthritis: diagnosis**

NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.

### **2010 American College of Rheumatology criteria**

Target population. Patients who

- 1) have at least 1 joint with definite clinical synovitis
- 2) with the synovitis not better explained by another disease

Classification criteria for rheumatoid arthritis (add score of categories A-D; a score of 6/10 is needed definite rheumatoid arthritis)

Key

- RF = rheumatoid factor
- ACPA = anti-cyclic citrullinated peptide antibody

Factor	Scoring
<b>A. Joint involvement</b>	
1 large joint	0
2 - 10 large joints	1
1 - 3 small joints (with or without involvement of large joints)	2
4 - 10 small joints (with or without involvement of large joints)	3
10 joints (at least 1 small joint)	5
<b>B. Serology (at least 1 test result is needed for classification)</b>	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
<b>C. Acute-phase reactants (at least 1 test result is needed for classification)</b>	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
<b>D. Duration of symptoms</b>	
< 6 weeks	0
> 6 weeks	1

Question 3 of 74

A 72-year-old woman presents to the emergency department because she is struggling to cope at home. She has noticed that she has been struggling to get out of bed over the last month and not been feeling herself. She denies any fevers or specific systemic symptoms other than feeling weak and tired and her arms have been feeling heavy in the morning. Both her shoulders have

been aching, and her appetite has been reduced. She has a past medical history of stroke, from which she made a complete recovery, atrial fibrillations, heart attack with coronary stenting and hypertension. Her observations are normal apart from a temperature of 37.7 degrees. Her joints are not tender and not swollen. She has normal power in her shoulders. Her visual acuity is normal.

Blood tests:

Hb	122 g/l
Platelets	$366 \times 10^9/l$
WBC	$8.9 \times 10^9/l$
Na <sup>+</sup>	137 mmol/l
K <sup>+</sup>	4.1 mmol/l
Urea	6.2 mmol/l
Creatinine	122 $\mu$ mol/l

What is the most likely diagnosis?

[Polymyalgia rheumatica84% Rheumatoid arthritis3% Dermatomyositis6% Osteoarthritis4% Adhesive capsulitis4%](#)

Polymyalgia rheumatic is characterised by abrupt onset of bilateral early morning stiffness in the over 50s

The most likely diagnosis is polymyalgia rheumatica due to the sudden onset of bilateral proximal difficulty in moving arms in a patient over 50 years old without weakness. This is commonly, but not always, described as a stiffness. These are some of the key features of polymyalgia rheumatica which help diagnosis, and the presence of loss of appetite, low-grade fever and morning symptoms are supportive. Dermatomyositis is a differential diagnosis that can be hard to exclude but the absence of rash, detectable weakness and muscle tenderness makes this unlikely. Rheumatoid arthritis would be unusual at this age without symmetrical polyarthritis but the acute onset makes it even less likely. Osteoarthritis normally affects hips and knees to a greater extent and would have a gradual onset without fever. Adhesive capsulitis is possible as a bilateral diagnosis but would need a reduced range of motion in both passive and active ranges and would not be as systemic as in this patient.

## **Polymyalgia rheumatica**

Pathophysiology

- overlaps with temporal arteritis



- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

### Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- aching, morning stiffness in proximal limb muscles (not weakness)
- also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

### Investigations

- ESR > 40 mm/hr
- note CK and EMG normal
- reduced CD8+ T cells

### Treatment

- prednisolone e.g. 15mg/od - dramatic response

### Question 4 of 74

A 25-year-old man presents to rheumatology clinic. He has been suffering from a stiff and painful lower back in the mornings and saw his GP who referred him to clinic. He has been suffering from this problem for five months and it has not been improving. He is normally fit and well and has no medical problems. He has a past medical history of asthma and eczema but both of these have improved through adolescence and he has required no treatment in the last five years. On examination, he appears well, and his joints are not swollen or painful. Flexion of his lumbar spine is slightly restricted. He is afebrile. What is the most appropriate investigation at this stage?

[Rheumatoid factor4%HLA-B2723%CT lumbar spine6%Pelvic X-ray51%MRI lumbar spine16%](#)

Diagnosis of ankylosing spondylitis can be best supported by sacro-ilitis on a pelvic X-ray. The likely diagnosis in this patient is ankylosing spondylitis. In a young man with lower back stiffness this is the most likely clinical diagnosis. The earliest evidence is sacroiliitis which is best confirmed on pelvic X-ray. Imaging of the lumbar spine can show changes which are typical for the condition but in the early stages sacroiliitis is a more reliable sign. HLA-B27 is not

sensitive enough to reliably exclude ankylosing spondylitis, whereas rheumatoid factor is not usually elevated.

## **Ankylosing spondylitis: investigation and management**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

### **Investigation**

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



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40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



© Image used on license from [Radiopaedia](#)



Ankylosing spondylitis with well formed syndesmophytes



© Image used on license from [Radiopaedia](#)



Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



© Image used on license from [Radiopaedia](#)



Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

## Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement

- the 2010 EULAR guidelines suggest: '*Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments*'
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

#### Question 5 of 74

A 35-year-old lady with diffuse systemic sclerosis attends the rheumatology clinic. She has had worsening arthralgia over the last 2 months, mainly in the hands and feet. She does not complain of any other symptoms.

On examination her blood pressure is 161/94 mmHg, her heart rate is 90 beats per minute and her oxygen saturations are 96% on room air. She has sclerodactyly and tender small joints of the hands and feet with mild swelling. The hands are pale and cool. Her chest is clear.

Her blood tests are as follows:

Hb	110 g/l	Na <sup>+</sup>	136 mmol/l	Bilirubin	5 µmol/l
Platelets	210 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.7 mmol/l	ALP	90 u/l
WBC	10 * 10 <sup>9</sup> /l	Urea	5 mmol/l	ALT	21 u/l
Neuts	7 * 10 <sup>9</sup> /l	Creatinine	89 µmol/l	γGT	30 u/l
Lymphs	2.5 * 10 <sup>9</sup> /l	ESR	99 mm/h	Albumin	32 g/l

Which drug should be used with caution in this patient?

[Tacrolimus 20%](#) [Azathioprine 12%](#) [Methotrexate 23%](#) [Mycophenolate mofetil 17%](#) [Prednisolone 28%](#)

Steroid use is known to precipitate scleroderma renal crisis and this is a patient who already has hypertension. Azathioprine, mycophenolate mofetil, tacrolimus and methotrexate are all immunosuppressive agents which may be used in rheumatological conditions, though methotrexate may cause additional pulmonary fibrosis.

Reference: Denton CP. Renal manifestations of systemic sclerosis - clinical features and outcome assessment. *Rheumatology* 2008;47:v54-v56.

## Systemic sclerosis



Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

#### Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

#### Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

#### Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear



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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

- Question 6 of 74
- A 68-year-old man presents with acute back pain. He has a past medical history of lung cancer and spinal metastases.

Investigation results are as follows:

Na<sup>+</sup> 138 mmol/l  
 K<sup>+</sup> 4.6 mmol/l  
 Urea 16.8 mmol/l  
 Creatinine 210 µmol/l  
 eGFR 22 µmol/l

- 

CT scan Pathological fractures of L2, L4 and L5

- 

What drug would you choose to prevent further pathological features?

- [Pamidronate21%Zoledronate30%Denosumab34%Raloxifene6%Strontium ranelate9%](#)
- 
- Bisphosphonates and denosumab can be used to prevent pathological fractures in bone metastases. If the eGFR < 30, denosumab is preferred
- Bisphosphonates are first line for prevention of pathological fractures. However they are contraindicated if eGFR is < 30.

Denosumab is recently licensed to prevent pathological fractures and can be used in patients with an eGFR < 30. NICE recommend that it is used as an option for preventing skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and from solid tumours other than breast and prostate if bisphosphonates would otherwise be prescribed. Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

- 

- 

- **Denosumab**

- 

Denosumab is a relatively new treatment for osteoporosis. It is a human monoclonal antibody that inhibits osteoclast formation, function and survival. Remember that osteoblasts build bone, osteoclasts eat bone. It is given as a subcutaneous injection, at a dose of 60mg, every 6 months.

A larger dose of denosumab (120mg) may also be given every 4 weeks for the prevention of skeletal-related events (i.e. pathological fractures) in adults with bone metastases from solid tumours. For example, you may have noticed some of your breast cancer patients

have been prescribed denosumab.

### **Where does it fit in the management of osteoporosis?**

Oral bisphosphonates are still given first-line, with oral alendronate being the first-line treatment. If alendronate is not tolerated then NICE recommend using an alternative bisphosphonate - either risedronate or etidronate. Following this the advice becomes more complicated with the next-line medications only being started if certain T score and other risk factor criteria being met. Raloxifene and strontium ranelate were recommended as next-line drugs in the NICE criteria but following recent safety concerns regarding strontium ranelate it is likely there will be an increasing role for denosumab.

NICE published a technology appraisal looking at the role of denosumab in 2010. A link is provided.

### **What are the known side-effects of denosumab?**

Denosumab is generally well tolerated. Dyspnoea and diarrhoea are generally considered the two most common side effects, occurring in around 1 in 10 patients. Other less common side effects include hypocalcaemia and upper respiratory tract infections.

### **What does the Drug Safety Update add?**

Cases of atypical femoral fractures have been noted in patients taking denosumab. Doctors are advised to look out for patients complaining of unusual thigh, hip or groin pain.

#### Question 1 of 68

62-year-old woman complains of knee pain. She has struggled with pain for several years. She finds that it gets worse through the day and is relieved by resting. She does not normally come and see doctors but the pain has gotten to the point where she would like additional treatment. She is not keen on surgery as of yet. She is known to have osteoarthritis. She has been taking paracetamol but not tried any other medication. What is the most appropriate strategy to further help relieve her pain?

[Codeine3%](#)[Oral NSAIDs19%](#)[Topical NSAIDs67%](#)[Intra-articular steroid injection9%](#)[Oral morphine3%](#)

The correct answer is topical NSAIDs. This is a case of managing pain in osteoarthritis. As she has knee osteoarthritis the first line of treatment can include paracetamol and topical NSAIDs.

Topical NSAIDs are only appropriate for osteoarthritis of the hands and knees. Second line treatment includes oral NSAIDs, codeine, capsaicin cream and intra-articular corticosteroids.

## **Osteoarthritis: management**

NICE published guidelines on the management of osteoarthritis (OA) in 2014

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- paracetamol and topical NSAIDs are first-line analgesics. Topical NSAIDs are indicated only for OA of the knee or hand
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, TENS and shock absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores
- more recent studies have however been mixed
- the 2008 NICE guidelines suggest it is not recommended
- a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

## **Question 2 of 68**

A 68-year-old gentleman presents acutely with a hot, red, swollen and painful right big toe. This has happened twice before, some years ago, and he has never sought medical attention. He has a raised serum urate level and joint fluid analysis demonstrates negatively birefringent needle-shaped crystals. Once symptoms settle he is started on allopurinol but develops a severe

hypersensitivity reaction to this. Which agent should be tried next as a long-term treatment option?

[Colchicine16% Naproxen6% Febuxostat67% Methotrexate5% Prednisolone7%](#)

Febuxostat is recommended as an option for the management of chronic hyperuricaemia in gout only for patients who are intolerant of allopurinol or for whom allopurinol is contra-indicated. For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant discontinuation, or to prevent full dose escalation for optimal effectiveness.

Watch out for severe hypersensitivity reactions (including Stevens-Johnson) with febuxostat, which would be a reason to discontinue this agent.

<https://www.ncbi.nlm.nih.gov/pubmed/21155617>

## **Gout: management**

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 450  $\mu\text{mol/l}$ )

### Acute management

- NSAIDs
- intra-articular steroid injection
- colchicine\* has a slower onset of action. The main side-effect is diarrhoea
- oral steroids may be considered if NSAIDs and colchicine are contraindicated. A dose of prednisolone 15mg/day is usually used
- if the patient is already taking allopurinol it should be continued

### Allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300  $\mu\text{mol/l}$
- NSAID or colchicine cover should be used when starting allopurinol

### Indications for allopurinol\*\*

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

### Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

### Other points

- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension
- calcium channel blockers also decrease uric acid levels, possibly by a renal vasodilatory effect
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels

\*inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

\*\*patients with Lesch-Nyhan syndrome often take allopurinol for life

### Question 3 of 68

A 77-year-old male presents to the Emergency Department with a two-day history of right temporal, throbbing headache, constant in nature and 8/10 severity. He reports this being the first ever episode of this headache and is different to his previous migraines, which have been typically in the left occipital region, lasting minutes, and fairly stereotyped over the past 60 years. Apart from migraines, he has no other medical history. On examination, his right scalp is tender and a prominent right temporal artery is noted. He is afebrile with no skin rashes. His blood tests are as follows:

Hb 138 g/l

Platelets  $552 \times 10^9/l$

WBC 11.5 \* 10<sup>9</sup>/l  
ESR 85 mm/hr

Na<sup>+</sup> 146 mmol/l  
K<sup>+</sup> 4.4 mmol/l  
Urea 9.6 mmol/l  
Creatinine 115 µmol/l  
CRP 23 mg/l

You empirically start him on 60mg prednisolone. He undergoes temporal artery biopsy within 24 hours of his admission demonstrating no signs of temporal arteritis.

What is the most appropriate next step?

[Repeat temporal artery biopsy19%Continue prednisolone but at reduced dose 10mg OD8%Discharge4%Continue prednisolone at 60mg65%Start anti-migraine medication4%](#)

All the clinical features point to right temporal arteritis. Remember that a negative temporal artery biopsy does not rule out temporal arteritis! Shorter lengths of biopsy or removal of a 'skip lesion' result in a 9% false negative rate. There is no indication for a repeat temporal artery biopsy on the same or contralateral side, an ultrasound temporal artery may be helpful instead. Someone who has clinical temporal arteritis should thus maintain on high dose prednisolone to protect their vision. This headache is clearly different from the patient's normal migraines; anti-migraine medication is thus inappropriate.

## Temporal arteritis

Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

### Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%)
- visual disturbances secondary to anterior ischemic optic neuropathy
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)



- also lethargy, depression, low-grade fever, anorexia, night sweats

### Investigations

- raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- temporal artery biopsy: skip lesions may be present
- note creatine kinase and EMG normal

### Treatment

- high-dose prednisolone - there should be a dramatic response, if not the diagnosis should be reconsidered
- urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible

### Question 1 of 65

A 65-year-old man presented to his General Practitioner with a 3-month history of bilateral shoulder aches and pains. The symptoms were associated with stiffness in the mornings taking up to two hours to resolve after waking. The patient denied any symptoms of headache, jaw claudication or visual disturbance. The patient had no symptoms of dry eyes or mouth, no skin or hair changes, no weight loss and no fevers.

Past medical history included hypertension and chronic obstructive pulmonary disease. Regular medications included ramipril, simvastatin and inhaled salbutamol as required. The patient was an ex-smoker who drank 25 units of alcohol per week. The patient had recently retired having spent his working life as a train driver.

The examination did not reveal any inflamed joints excepting slight tenderness across the shoulder girdle. There was no evidence of scalp tenderness. The cardiovascular and respiratory examination was unremarkable.

Investigations requested by the General Practitioner are listed below.

Haemoglobin	134 g / L
White cell count	$7.5 \times 10^9/l$
Neutrophils	$6.0 \times 10^9/l$
Platelets	$356 \times 10^9/l$

Urea	8.9 mmol / L
Creatinine	110 micromol / L
Sodium	132 mmol / L
Potassium	4.9 mmol / L
Erythrocyte sedimentation rate	85 mm / h
Rheumatoid factor	Negative
Creatinine kinase	121 U / L (reference 5-130)
Calcium (adjusted)	2.25 mmol / L (reference 2.18-2.58)
Alkaline phosphatase	67 U / L (reference 35-100)
Thyroid stimulating hormone	2.5 microU / L
Protein electrophoresis	Normal

What is the appropriate next management step for this patient?

[Stop statin therapy and review in 6 weeks11%](#)[Ultrasound study of shoulders and hips6%](#)[Referral for specialist rheumatology opinion13%](#)[Prednisolone 15 mg daily with dose tapering over 2 years46%](#)[Prednisolone 40 mg daily with dose tapering over 1 year24%](#)

This patient presents with a classical history for polymyalgia rheumatica and a raised ESR. There are no factors in the history or investigations that suggest an alternative diagnosis (for example, giant cell arteritis, other connective tissue disease, myeloma, malignancy or occult infection). The normal CK would make statin-induced myopathy unlikely.

In such cases, a trial of steroid therapy for likely polymyalgia rheumatica is appropriate. The diagnosis will be confirmed by rapid resolution of symptoms following initiation of treatment. Observational studies suggest a typical starting dose of prednisolone around 15 mg with a median time to stopping therapy of two years.

Musculoskeletal ultrasound often identifies inflammation around the shoulders and hips although these findings are not unique to polymyalgia rheumatica. The usefulness of this technique is yet to be determined outside of specialist settings.

Mackie S, Mallen C. Polymyalgia rheumatica. BMJ 2013;347:f6937

## **Polymyalgia rheumatica**

Pathophysiology

- overlaps with temporal arteritis
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

### Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- aching, morning stiffness in proximal limb muscles (not weakness)
- also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

### Investigations

- ESR > 40 mm/hr
- note CK and EMG normal
- reduced CD8+ T cells

### Treatment

- prednisolone e.g. 15mg/od - dramatic response

### Question 2 of 65

A 26-year-old woman presents with a four month history of back pain. The pain is located around the lower lumbar vertebrae and spreads to both buttocks. Ibuprofen and walking seem to improve the pain. A lumbar spine film is requested:



© Image used on license from [Radiopaedia](#)



What is the most likely cause of this patient's back pain?

[Marble bone disease](#)4% [Discitis](#)6% [Ankylosing spondylitis](#)80% [Facet-joint dysfunction](#)7% [Rheumatoid arthritis](#)3%

Ankylosing spondylitis with well formed syndesmophytes are seen on the lumbar spine film.

The first thing to address is the sex of the patient. Of course ankylosing spondylitis is more common in men but the male-to-female ratio is only 3:1. This means it is reasonable to be asked about female patients in questions, particularly if there is accompanying 'hard evidence' such as x-rays.

Marble bone disease (osteopetrosis) results in dense, thick bones that are prone to fracture. Syndesmophytes are not a feature.

Facet-joint dysfunction is a common cause of back pain but it would not explain the x-ray findings.

Rheumatoid arthritis of course does not commonly present with back pain. The following x-ray changes are typically seen:

- loss of joint space

- juxta-articular osteoporosis
- soft-tissue swelling
- periarticular erosions
- subluxation

## **Ankylosing spondylitis: investigation and management**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

### **Investigation**

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



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40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



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Ankylosing spondylitis with well formed syndesmophytes



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Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine





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Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



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Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

## Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement

- the 2010 EULAR guidelines suggest: *'Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments'*
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

### Question 3 of 65

An 80-year-old retired GP with no past medical history presents to hospital with a 6 month history of muscle aches and weakness. She also has difficulty swallowing and has had 3 courses of antibiotics for a presumed chest infection in the last 3 months. In the last 2 days she has been struggling to cope at home and has had two falls.

Blood tests show :

Erythrocyte Sedimentation Rate (ESR) 60 mm/hour g/l

Creatinine Kinase 8000 U/L

Which of the following blood tests would be LEAST helpful in the work up?

[Autoimmune profile7%FBC8%AST and ALT17%Urine myoglobin16%Renal biopsy52%](#)

This lady seems to have polymyositis. An autoimmune profile is useful as ANA is positive in one third of patients. Anti-Jo antibodies are positive in 20% of patients and indicate a poorer prognosis with interstitial lung disease. A full blood count may show leukocytosis or thrombocytosis. AST/ALT are both muscle enzymes that will be elevated. Creatinine kinase will also be elevated along with urine myoglobin. In some cases the patient may develop renal impairment from rhabdomyolysis and thus U+Es should be monitored. Renal biopsy would not be diagnostically helpful in this situation.

## Polymyositis

### Overview

- inflammatory disorder causing symmetrical, proximal muscle weakness
- thought to be a T-cell mediated cytotoxic process directed against muscle fibres
- may be idiopathic or associated with connective tissue disorders

- associated with malignancy
- dermatomyositis is a variant of the disease where skin manifestations are prominent, for example a purple (heliotrope) rash on the cheeks and eyelids
- typically affects middle-aged, female:male 3:1

## Features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

## Investigations

- elevated creatine kinase
- EMG
- muscle biopsy
- anti-Jo-1 antibodies are seen in pattern of disease associated with lung involvement, Raynaud's and fever

## Question 4 of 65

A 36-year-old man presents with progressive lower back pain for the past six months. The pain is worse in the mornings and tends to ease with exercise and the passage of the day. He has tried paracetamol but this does not fully controlled his pain. An x-ray of his spine is shown below:



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What is the most appropriate first-line treatment

[Methotrexate7%](#)[Sulfasalazine6%](#)[Naproxen76%](#)[Vitamin D supplementation4%](#)[Infliximab7%](#)

The x-ray shows syndesmophytes and squaring of vertebral bodies consistent with a diagnosis of ankylosing spondylitis.

NSAIDs are the first-line drug treatment in an ankylosing spondylitis. Regular exercise is also very important. The role of anti-TNF therapies is increasing but they are not currently first-line and the 2008 NICE guidelines specifically advise against using infliximab.

**Ankylosing spondylitis: investigation and management**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

### **Investigation**

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



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40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



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Ankylosing spondylitis with well formed syndesmophytes





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Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



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Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



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Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

## Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement

- the 2010 EULAR guidelines suggest: '*Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments*'
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

#### Question 5 of 65

A 37-year-old woman with known rheumatoid arthritis was reviewed at her annual follow-up at rheumatology clinic. The diagnosis of rheumatoid arthritis had been made ten years previously after the patient experienced severe inflammation of her meta-carpal phalangeal joints of both hands. Symptoms had been controlled with an initial reducing course of oral steroids and had been subsequently maintained on 15 mg of subcutaneous methotrexate weekly. She had experience one significant flare of her symptoms 18 months previously that had necessitated a single intra-muscular dose of corticosteroids.

On this occasion, the patient reported no further swelling, pain or redness of the joints of her hands or other joints. She did report however that over the past 6 months she had experienced on-going severe pains throughout her body. In addition, she had been feeling tired and lethargic and had been finding it hard to concentrate on her work at as a computer programmer. She denied any history of skin rashes, photosensitivity, hair loss, swallowing difficulties or dry eyes and she had not lost any weight.

The examination did not demonstrate any evidence of active synovitis. A minor ulnar deviation of the digits of both hands was noted which the patient denied caused her any functional impairment. The patient was noted to be tender on palpation of the muscles of her arms, legs and paraspinal muscles. However, there was no associated muscle weakness with patient able to rise unaided from a chair without using the assistance of her arms. There was no thickening of the skin of the hands or face. The cardiovascular, respiratory and abdominal examination was unremarkable and there were no skin rashes.

Investigations requested following clinic review are listed below.

Haemoglobin	134 g / L
White cell count	$6.6 \times 10^9/l$
Platelets	$198 \times 10^9/l$
Sodium	139 mmol / L
Potassium	4.3 mmol / L
Urea	4.8 mmol / L
Creatinine	75 micromol / L
Erythrocyte sedimentation rate	15 mm / h

Rheumatoid factor	Positive
Anti-nuclear antigen	Negative
Anti-citrullinated protein antibodies	37 units (reference < 20)

What is the likely cause of the patient's new symptoms?

[Flare of rheumatoid arthritis10%Mixed connective tissue disease11%Chronic regional pain syndrome10%Inclusion body myositis8%Fibromyalgia60%](#)

The patient has chronic widespread pain associated with lethargy and difficulty concentrating and multiple tender points on palpation. The patient has immunological results consistent with her previous diagnosis of rheumatoid arthritis but no clinical or biochemical evidence of a flare of this disease or the development of a new connective tissue disease or myositis. Chronic regional pain syndrome is associated with persistent burning pain in one limb, usually after a minor injury.

The patient's symptoms are consistent with the diagnostic entity known as fibromyalgia. It is important to be aware that fibromyalgia is not a diagnosis of exclusion and can co-exist with other diseases as in this case.

Carnes D, Underwood M, Rahman A. Fibromyalgia. BMJ 2014;348:g474.

## **Fibromyalgia**

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

### **Epidemiology**

- women are 10 times more likely to be affected
- typically presents between 30-50 years old

### **Features**

- chronic pain: at multiple site, sometimes 'pain all over'
- lethargy
- sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which lists 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007 and also a BMJ review in 2014.

- explanation
- aerobic exercise: has the strongest evidence base
- cognitive behavioural therapy
- medication: pregabalin, duloxetine, amitriptyline

#### Question 1 of 60

A 63-year-old female presents to gastroenterology outpatient clinic with a four-week history of gastric reflux, which has not improved despite being prescribed both ranitidine and omeprazole by her GP. She is awaiting an urgent OGD to investigate symptoms further. She reports having lost 7kg in weight over the past 6 months and is also distressed by appearances of white hard lumps appearing on her fingertips. On examination, you note cool peripheries and dry mucous membranes, left thumb calcinosis surrounded by shiny skin up to her wrist joint and wrinkling of skin around her mouth. Her blood tests are as follows demonstrate she is positive for anticentromere antibodies. What is the most likely diagnosis?

[Diffuse cutaneous systemic sclerosis15%](#)[Systemic sclerosis sine scleroderma12%](#)[Zollinger-Ellison syndrome5%](#)[Limited cutaneous systemic sclerosis 64%](#)[Raynaud's syndrome4%](#)

Systemic sclerosis (SS) is a fairly clear answer when presented with a combination of sclerodactyly, calcinosis, perioral puckering and gastro-oesophageal reflux symptoms in a middle-aged female. The main differentials are whether this represents diffuse cutaneous, limited cutaneous or systemic sclerosis sine scleroderma. The latter describes patients with systemic involvement and possible Raynaud's phenomenon in the absence of other cutaneous manifestations with detection of SS autoantibodies. SS can be described generally as diffuse when skin proximal to the distal forearm is involved, such as the elbow, thorax or abdomen. Note that both limited and diffuse cutaneous SS has extracutaneous involvement: however, patients with diffuse cutaneous SS are more likely to develop significant renal, lung and cardiac disease.

Autoantibodies are useful in confirming the subtype of SS and predict extracutaneous

involvement but negative results do not rule out SS. Anti-centromere antibodies are associated with limited cutaneous SS1, anti-Scl 70 with diffuse SS and lung involvement<sup>1</sup>, anti-RNA polymerase III to those at high risk of scleroderma renal crisis<sup>2</sup>, anti-U3-RNP to those at high risk of pulmonary hypertension<sup>3</sup> and anti-PM-Scl to those at high risk of SS associated myositis<sup>4</sup>.

1. Reveille JD, Solomon DH et al. Evidence-based guidelines for the use of immunologic tests: anticentromere, Scl-70, and nucleolar antibodies. *Arthritis Rheum.* 2003;49(3):399

2. Nguyen B, Mayes MD, Arnett FC et al. HLA-DRB1\*0407 and \*1304 are risk factors for scleroderma renal crisis. *Arthritis Rheum.* 2011;63(2):530.

3. Sacks DG, Okano Y, Steen VD et al. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. *J Rheumatol.* 1996;23(4):639

4. Oddis CV, Okano Y, Rudert WA et al. Serum autoantibody to the nucleolar antigen PM-Scl. Clinical and immunogenetic associations. *Arthritis Rheum.* 1992;35(10):1211

## **Systemic sclerosis**

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

### **Limited cutaneous systemic sclerosis**

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

### **Diffuse cutaneous systemic sclerosis**

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

## Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear



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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

## Question 2 of 60

A 65-year-old woman is seen in the rheumatology clinic. She has complained about 'arthritis' in her hands and feet for many years:



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What is the most likely diagnosis?

[Paget's disease](#)5% [Primary hyperparathyroidism](#)8% [Rheumatoid arthritis](#)57% [Osteoarthritis](#)20% [Gout](#)10%

The distribution of joint problems (mainly metacarpophalangeal and proximal interphalangeal joints) and changes seen (erosions, subluxation and loss of joint space) points to a diagnosis of rheumatoid arthritis.

### **Rheumatoid arthritis: x-ray changes**

Early x-ray findings

- loss of joint space
- juxta-articular osteoporosis
- soft-tissue swelling

### Late x-ray findings

- periarticular erosions
- subluxation

### Question 3 of 60

A 33 year-old man from Turkey presents with a 24 hour history of abdominal pain and fever. The pain is generalised, 8/10 on the pain scale and is constant. There is no evidence of jaundice or organomegaly and bowel sounds are present. He does not know of any family history as he is adopted and does not take any regular medication. Examination reveals guarding and a temperature of 38.9°C, blood pressure 160/90 mmHg and a pulse rate of 95 beats per minute. His previous history includes two admissions in the past for abdominal pain, although the exact cause of this was not known.

Abdominal imaging does not show anything remarkable and his symptoms resolve after 30 hours. What is the most appropriate management for this condition?

[Indomethacin14%](#)[Corticosteroids17%](#)[Diclofenac9%](#)[Co-dydramol9%](#)[Colchicine51%](#)

This patient has presented with Familial Mediterranean Fever, which typically presents with multiple episodes of severe abdominal pain and pyrexia. Colchicine is very effective in treating episodes of abdominal pain and fever and can be used as both a treatment and preventive for the condition, provided adequate stomach protection is prescribed.

### **Familial Mediterranean Fever**

Familial Mediterranean Fever (FMF, also known as recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is more common in people of Turkish, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- pyrexia
- abdominal pain (due to peritonitis)
- pleurisy

- pericarditis
- arthritis
- erysipeloid rash on lower limbs

## Management

- colchicine may help

## Question 4 of 60

A 54-year-old woman presents to the medical clinic with an itchy rash. She says that she has noticed a bluish-purple patchy rash mostly on sun-exposed areas. On examination, she has purple eyelids and rough raised purple areas on her knuckles. Her nails show ragged cuticles, and blood vessels are seen on the nail fold. A purple, poorly defined rash is present on both her arms going up to her shoulders. What is the likely diagnosis?

[Dermatomyositis61%](#)[Discoid lupus10%](#)[SLE5%](#)[Lichen planus11%](#)[Lupus pernio12%](#)

The correct answer is dermatomyositis. The patient has a photosensitive rash, as well as a heliotrope rash around the eyelids, and a description of Gottron's papules. The distribution is also in keeping with a dermatomyositis rash. Lupus would normally have a macular erythematous and photosensitive butterfly rash over the face, and there can be a history of joint and neurological involvement. Lichen planus is a violaceous and itchy rash in patches, with a distribution similar to psoriasis.

## Dermatomyositis

### Overview

- an inflammatory disorder causing symmetrical, proximal muscle weakness and characteristic skin lesions
- may be idiopathic or associated with connective tissue disorders or underlying malignancy (typically ovarian, breast and lung cancer, found in 20-25% - more if patient older)
- polymyositis is a variant of the disease where skin manifestations are not prominent

## Skin features

- photosensitive
- macular rash over back and shoulder
- heliotrope rash in the periorbital region
- Gottron's papules - roughened red papules over extensor surfaces of fingers
- nail fold capillary dilatation

## Other features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

## Investigations

- the majority of patients are ANA positive, with around 25% anti-Mi-2 positive

## Question 5 of 60

A 41-year-old woman presents with tightening of fingers, mild difficulty swallowing, and mild shortness of breath on exertion. She takes pantoprazole for reflux. On examination there is tightening of skin in her fingers, however the rest of the skin is normal. Her joints are not inflamed. The rest of her examination was normal (including chest examination). Her chest X-ray is also normal. There is mild decrease in DLCO on lung function tests. Which of the following antibodies are indicative of the underlying diagnosis?

[Anti-Scl-70 antibody 27%](#) [Anti-dsDNA antibody 3%](#) [Rh factor antibody 2%](#) [Anti-centromere antibody 65%](#) [Anti-Jo-1 antibody 3%](#)

The underlying diagnosis is limited scleroderma. Limited scleroderma has tightened hard skin below the elbows. Dysphagia and some lung fibrosis occurs in both limited and diffuse scleroderma. Limited scleroderma is associated with anti-centromere antibody with Anti-scl-70 antibody associated with diffuse scleroderma. Diffuse scleroderma is characterised by lesions proximal to the elbow, trunk and face (limited can have some facial involvement). Limited scleroderma has a 90% 5-year survival, diffuse scleroderma 70% 5-year survival. In the past, renal crises were the most common cause of death in patients with scleroderma. Aggressive

treatment with blood pressure lowering drugs, particularly those known as ACE inhibitors, is proving to be successful in reducing this risk.

Anti-dsDNA and Rh factor are indicative of SLE an RA/Sjogrens/others, but there is no evidence of arthritis or cutaneous rashes. Anti-Jo-1 antibody is a marker of polymyositis.

## **Systemic sclerosis**

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

Limited cutaneous systemic sclerosis

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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

## Question 6 of 60

A 68-year-old female accountant on azathioprine for systemic lupus erythematosus (SLE) presented to the rheumatology clinic for her usual yearly follow up. She is clinically well and her blood investigations show stable disease but you note raised serum uric acid. She also volunteers that she intermittently suffers excruciatingly painful, red and swollen joints including her left first metatarsophalangeal joint and right ankle. These episodes improve with diclofenac. She is currently asymptomatic. Based on her symptoms you strongly suspect that she suffers from recurrent episodes of gout.

In the management of gout in this patient, which of the following prescription medications should you strongly avoid?

[Diclofenac7%](#) [Allopurinol59%](#) [Colchicine13%](#) [Probenecid16%](#) [Prednisolone6%](#)

Based on her current complaints, this patient has recurrent episodes of gout and needs



prophylactic treatment as well as treatment during acute attacks.

All the listed medications can be used in the management of gout but the one to strongly avoid is allopurinol. Allopurinol is a common medication used for gout prophylaxis but in this patient who is taking azathioprine, allopurinol should not be prescribed concurrently.

Allopurinol inhibits xanthine oxidase an enzyme involved in the metabolism of azathioprine. Azathioprine is normally converted to 6-mercaptopurine (6-MP), it's active form. 6-MP is then broken down by xanthine oxidase. Following inhibition of this enzyme by allopurinol, 6-MP accumulates. This could cause severe bone marrow suppression.

## **Azathioprine**

Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis. A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.

Adverse effects include

- bone marrow depression
- nausea/vomiting
- pancreatitis

A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.

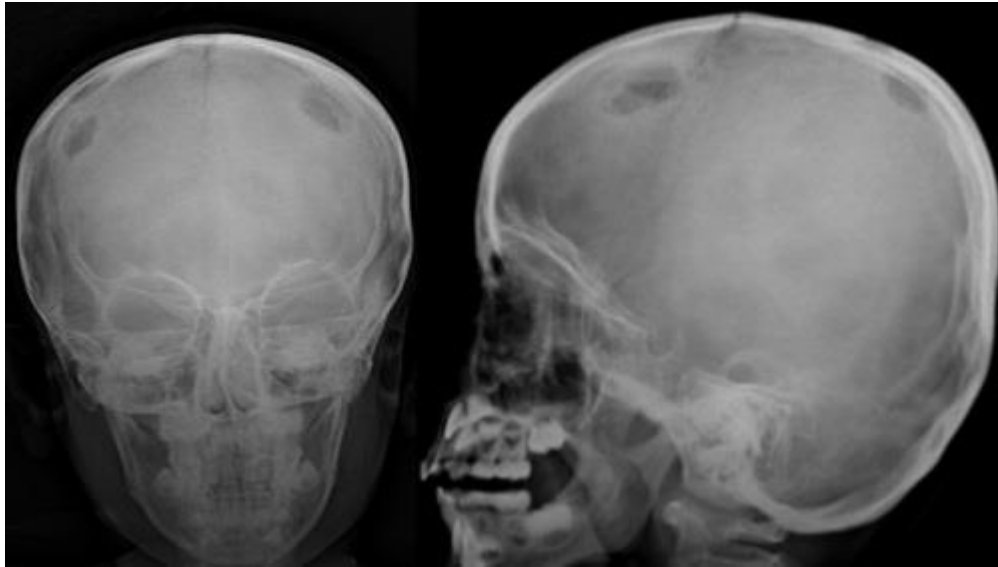
### **Question 7 of 60**

A 7-year-old girl who has recently emigrated from Turkey is brought to the Emergency Department with pain on walking and multiple swellings over her head. She also complains of persistent headaches which are now quite distracting and causing her to miss school. This symptoms have been getting gradually worse for the past few weeks.

She has a past medical history of eczema and asthma which is well controlled with a salbutamol inhaler as required. There is no family history of similar problems.

On examination a number of soft tissue swellings are noted on the scalp. She also has non-specific tenderness over the proximal part of the left femur.

A skull x-ray is requested:



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What is the most likely diagnosis?

[Multiple myeloma](#)8%[Langerhans cell histiocytosis](#)49%[Neurofibromatosis](#)8%[Systemic mastocytosis](#)17%[Wiskott-Aldrich syndrome](#)18%

The age of the patient combined with 'punched out' osteolytic skull lesions make a diagnosis of Langerhans cell histiocytosis likely.

Systemic mastocytosis results from a neoplastic proliferation of mast cells and is associated with urticaria pigmentosa and flushing.

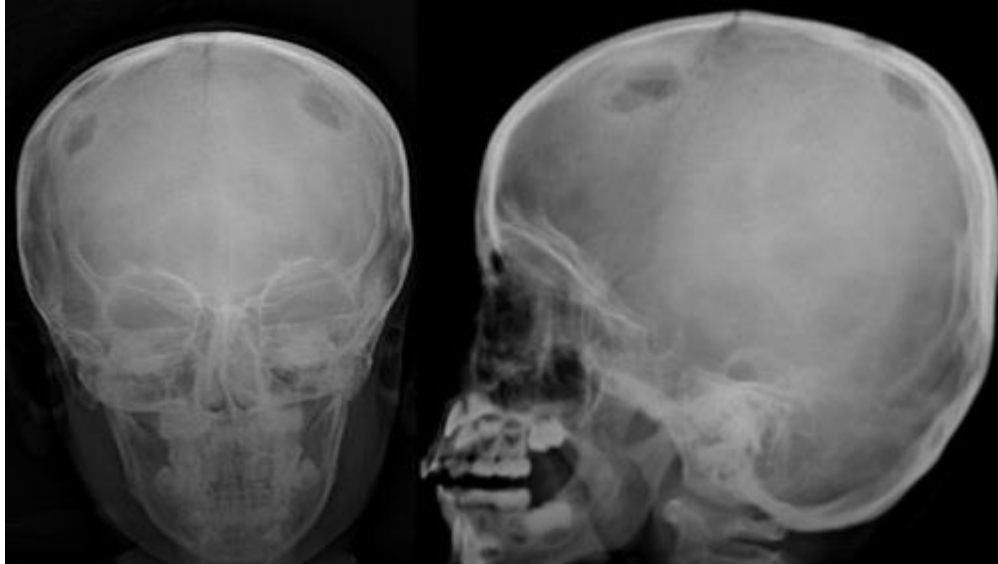
### **Langerhans cell histiocytosis**

Langerhans cell histiocytosis is a rare condition associated with the abnormal proliferation of histiocytes. It typically presents in childhood with bony lesions.

#### **Features**

- bone pain, typically in the skull or proximal femur

- cutaneous nodules
- recurrent otitis media/mastoiditis
- tennis racket-shaped Birbeck granules on electromicroscopy



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Young girl with multiple well defined 'punched out' osteolytic lesions with scalloped edges (geographic skull) are seen in the bilateral parietal regions. The lesions have a characteristic bevelled edge.

#### Question 8 of 60

A 24-year-old man has attended ED with severe abdominal pain. He has had 6 similar episodes this year, associated with bloating and diarrhoea that can last a few days at a time. During episodes he is afebrile. He has no significant medical history.

On examination you note he has right lower quadrant tenderness, but no guarding. He has multiple painful mouth ulcers and states he has previously had ulcers on his scrotum. On his shins, you note tender red and purple papules.

Bloods are as follows:

Hb	120 g/l	Na <sup>+</sup>	140 mmol/l
Platelets	270 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.0 mmol/l
WBC	6.6 * 10 <sup>9</sup> /l	Urea	3 mmol/l

Neuts  $4.2 \times 10^9/l$  Creatinine  $78 \mu\text{mol/l}$   
Lymphs  $1.0 \times 10^9/l$  CRP  $1 \text{ mg/l}$   
Eosin  $0.1 \times 10^9/l$

Which of the following would be most suggestive of the likely diagnosis?

[HLA-B27 allele 22% Positive faecal calprotectin 24% Pathergy reaction 42% MEFV gene mutation 8% Oocytes in stool 4%](#)

A positive pathergy test is suggestive of Behcet's syndrome

This man has presented with multiple episodes of abdominal pain, erythema nodosum and orogenital ulcers. This is a classical presentation of Behçet's disease.

Behçet's disease is associated with HLA-B51 and can present with an array of symptoms. As well as those listed above; neuropsychiatric symptoms, venous thromboembolism, arthritis and uveitis also frequently occur.

Diagnosis is made clinically, but a pathergy reaction is suggestive. This can be observed by making a small pin-prick in the skin to see if a lesion or ulcer forms. It is similar to the Koebner phenomenon and occurs in Behçet's disease and pyoderma gangrenosum.

HLA-B27 is associated with seronegative spondyloarthropathies. MEFV gene mutations are found in patients with familial Mediterranean fever, a condition that can also cause paroxysms of abdominal pain and tenderness. However, ulcers are uncommon and fevers are almost always present in attacks (as well as high levels of CRP).

Faecal calprotectin would be raised in inflammatory bowel disease. Crohn's disease can indeed cause erythema nodosum and mouth ulcers, but genital ulcers are uncommon.

Stool microscopy for oocytes would identify an underlying parasitic infection. This might also cause an eosinophilia.

## **Behcet's syndrome**

Behcet's syndrome is a complex multisystem disorder associated with presumed autoimmune mediated inflammation of the arteries and veins. The precise aetiology has yet to be elucidated however. The classic triad of symptoms are oral ulcers, genital ulcers and anterior uveitis

### **Epidemiology**

- more common in the eastern Mediterranean (e.g. Turkey)

- more common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men)
- tends to affect young adults (e.g. 20 - 40 years old)
- associated with HLA B5\* and MICA6 allele
- around 30% of patients have a positive family history

## Features

- classically: 1) oral ulcers 2) genital ulcers 3) anterior uveitis
- thrombophlebitis
- arthritis
- neurological involvement (e.g. aseptic meningitis)
- GI: abdo pain, diarrhoea, colitis
- erythema nodosum, DVT

## Diagnosis

- no definitive test
- diagnosis based on clinical findings
- positive pathergy test is suggestive (puncture site following needle prick becomes inflamed with small pustule forming)

\*more specifically HLA B51, a split antigen of HLA B5

## Question 9 of 60

A 23-year-old Sri Lankan male presents with 6 months of gradual onset low back pain, worse before waking. He describes increasing stiffness in his right wrist and left third metacarpal joints. On examination, you note reduced spinal movements in lateral spinal flexion and rotation and a positive Schober's test. He has not received any previous treatments for his back pain and has no other past medical history. What is the most appropriate initial management?

[Start sulphasalazine6%](#)[Start infliximab4%](#)[Start etanercept5%](#)[Physiotherapy and NSAIDs81%](#)[No treatment3%](#)

The patient gives a classic description of new onset ankylosing spondylitis. He presents from the typical age group of between 15-25. NSAIDs and physiotherapy should be the first line treatment for all symptomatic AS patients, allowing up to 4 weeks for assessment of effect. Up to 70% of

AS patients receive sufficient symptomatic relief with NSAIDs alone, with the most recent EULAR guidelines recommending continuous NSAIDs therapy for those with active persistent symptoms<sup>1</sup>. There is also evidence that this reduces radiological progression of the disease.

Systemic glucocorticoids have no place for AS management but intra-articular steroid injections may be indicated in peripheral joints or enthesitis. Of traditional DMARDs, sulphasalazine is the only DMARD with evidence of efficacy in peripheral joint involvement but is not effective in those with axial joint involvement<sup>2</sup>. TNF-alpha inhibitors are recommended on those with AS symptoms insufficiently controlled by NSAIDs alone. There appears to be no difference in efficacy between etanercept, infliximab or adalimumab<sup>3</sup>.

1. Zochling J, van der Heijde D, Burgos-Vargas R et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis*. 2010;65(4):442

2. Van der Heijde D, Sieper J, Maksymowych WP et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(6):905

3. McLeod C, Bagust A, Boland A et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(28):1

## **Ankylosing spondylitis: investigation and management**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

### **Investigation**

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



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40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



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Ankylosing spondylitis with well formed syndesmophytes





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Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



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Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



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Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

## Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement

- the 2010 EULAR guidelines suggest: '*Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments*'
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

#### Question 10 of 60

A 31-year-old female presents with abdominal pain. She reports a fever at home and last opened her bowels 3 days ago. She has vomited twice. On examination, she is alert and well-oriented. She has a diffusely tender but non-distended abdomen.

When asked about her past medical history she says she is generally well but has had occasional joint pains in the past which she attributes to wear and tear. She had an appendectomy at the age of 18, a diagnostic laparoscopy aged 25, and a cholecystectomy aged 29. She has been previously investigated for renal colic in the past but no stones have been identified on CT imaging.

Her blood results are as follows:

Hb	105 g/l	Na <sup>+</sup>	133 mmol/l
Platelets	445 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.9 mmol/l
WBC	10.4 * 10 <sup>9</sup> /l	Urea	4.5 mmol/l
Neuts	8.5 * 10 <sup>9</sup> /l	Creatinine	78 µmol/l
Lymphs	1.0 * 10 <sup>9</sup> /l	CRP	22 mg/l
Eosin	0.1 * 10 <sup>9</sup> /l	beta HCG	undetectable

An urgent abdominal plain film shows some faecal loading in the large bowel which is 4.5cm at widest point. There is air in the rectum.

How should this patient be managed?

[ERCP3% Urgent CT scan and wide bore NG tube20% Oral ofloxacin plus metronidazole for 14 days6% Urinary porphyrins33% Analgesia and colchicine37%](#)

The long surgical history in this relatively young patient should raise a suspicion of familial Mediterranean fever. Constipation can be a feature of acute attacks.

The normal bloods and X-ray make acute bowel obstruction somewhat less likely, and the history does not quite fit for pelvic inflammatory disease or acute intermittent porphyria.

## Familial Mediterranean Fever

Familial Mediterranean Fever (FMF, also known as recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is more common in people of Turkish, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- pyrexia
- abdominal pain (due to peritonitis)
- pleurisy
- pericarditis
- arthritis
- erysipeloid rash on lower limbs

## Management

- colchicine may help

## Question 1 of 50

A 68-year-old female diagnosed with rheumatoid arthritis four years ago presents gradually increasing tenderness in the small joints of both hands over the past 5 months. She continues to work as a legal secretary, involving significant amounts of time at a computer. She is currently on maximum doses of methotrexate and sulphasalazine on diagnosis and maintained on the same doses since. Her DAS score today is 5.8, it was 4.7 when you saw her in clinic last 1 month ago. What is the next management step?

[Continue methotrexate and sulphasalazine. Short-course oral prednisolone48%Stop current DMARDs. Start etanercept19%Stop current DMARDs. Start infliximab20%Admit for pulsed intravenous methylprednisolone5%Prescribe regular long-term celecoxib in addition to methotrexate and sulphasalazine8%](#)

Current NICE guidelines recommend the starting of biologic therapy when the patient has been on at least two DMARDs, including methotrexate, reporting two DAS 28 scores of greater than 5.1 at least one month apart<sup>1</sup>. A short course of oral prednisolone may be appropriate for flares for symptomatic control. However, this is not an option if the patient does not wish to take any

steroids. Intravenous pulsed steroids or long-term treatments are not appropriate. Regular COX-2 inhibitors are not recommended by NICE guidelines. NSAIDs are appropriate for short-term symptomatic control but only at lowest doses for as short a period as possible.

1. NICE Clinical Guideline 79. The management of rheumatoid arthritis in adults. Jan 2009

## **Rheumatoid arthritis: management**

The management of rheumatoid arthritis (RA) has been revolutionised by the introduction of disease-modifying therapies in the past decade. NICE has issued a number of technology appraisals on the newer agents and released general guidelines in 2009.

Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible. Other important treatment options include analgesia, physiotherapy and surgery.

### **Initial therapy**

- in the 2009 NICE guidelines it is recommended that patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids)

### **DMARDs**

- methotrexate is the most widely used DMARD. Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- sulfasalazine
- leflunomide
- hydroxychloroquine

### **TNF-inhibitors**

- the current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- etanercept: recombinant human protein, acts as a decoy receptor for TNF- $\alpha$ , subcutaneous administration, can cause demyelination, risks include reactivation of tuberculosis
- infliximab: monoclonal antibody, binds to TNF- $\alpha$  and prevents it from binding with TNF receptors, intravenous administration, risks include reactivation of tuberculosis

- adalimumab: monoclonal antibody, subcutaneous administration

### Rituximab

- anti-CD20 monoclonal antibody, results in B-cell depletion
- two 1g intravenous infusions are given two weeks apart
- infusion reactions are common

### Abatacept

- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion
- not currently recommended by NICE

### Question 1 of 49

A 32-year-old gentleman presented to his GP with an 8-week history of debilitating pain in his oral cavity and in his groin area. He had presented on numerous occasions to his GP with episodes of tiredness and non-specific malaise which each time was put down to non-specific viral illness. Eight months ago he was investigated by a gastroenterologist having presented with bloody diarrhoea and abdominal pain. He was diagnosed with a non-specific colitis of unknown origin which resolved spontaneously. He also suffered a solitary DVT of his left leg 6 years ago which was treated with oral anticoagulation. He smoked 20 cigarettes per day and consumed 20 units of alcohol per week. He was on no regular medication. Upon specific questioning, he denied joint pain or swelling. He also denied the presence of back pain. He was unaware of any family history as he was adopted from birth.

On examination, he appeared pale. His heart rate was 88 and blood pressure 118/78 mmHg. Examination of his cardiovascular system was unremarkable. Examination of his abdomen was likewise unremarkable. Examination of his oral mucosa revealed the presence of multiple aphthous ulceration. Examination of his external genitalia likewise revealed the presence of multiple shallow ulcers within his groin region. Examination of his joints was unremarkable.

Initial investigations revealed the following results:

Hb	139 g/l
Platelets	$333 \times 10^9/l$
WBC	$5.1 \times 10^9/l$
ESR	22 mm/hr

CRP	28 mg/l
Rheumatoid factor	negative
Anti CCP	negative
ANA	negative
HLA B27	positive

What is the most likely underlying diagnosis?

[Seronegative arthritis7%Disseminated gonococcal infection6%Crohn's disease8%Coeliac disease6%Behcet's syndrome73%](#)

This gentleman presents with a combination of malaise, oral and genital ulceration, colitis and iritis. Of the above options, Behcet's syndrome is the only option that unifies this combination. Note that HLA B27 is positive in 10 % of the population in the absence of seronegative arthritis. Crohn's disease may present with a colitis and aphthous ulceration as well as iritis, but it would be difficult to account for the past deep vein thrombosis.

## **Behcet's syndrome**

Behcet's syndrome is a complex multisystem disorder associated with presumed autoimmune mediated inflammation of the arteries and veins. The precise aetiology has yet to be elucidated however. The classic triad of symptoms are oral ulcers, genital ulcers and anterior uveitis

### **Epidemiology**

- more common in the eastern Mediterranean (e.g. Turkey)
- more common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men)
- tends to affect young adults (e.g. 20 - 40 years old)
- associated with HLA B5\* and MICA6 allele
- around 30% of patients have a positive family history

### **Features**

- classically: 1) oral ulcers 2) genital ulcers 3) anterior uveitis
- thrombophlebitis
- arthritis
- neurological involvement (e.g. aseptic meningitis)
- GI: abdo pain, diarrhoea, colitis



- erythema nodosum, DVT

## Diagnosis

- no definitive test
- diagnosis based on clinical findings
- positive pathergy test is suggestive (puncture site following needle prick becomes inflamed with small pustule forming)

\*more specifically HLA B51, a split antigen of HLA B5

## Question 2 of 49

A 26-year-old bilateral renal transplant recipient presents with pancytopenia. You work in a busy district general hospital and your consultant asks you to discuss with the renal specialists at your local tertiary centre for advice.

Hb 95 g/l

Platelets  $20 \times 10^9/l$

WBC  $1.2 \times 10^9/l$

Which one of the following medications is known to cause pancytopenia?

[Mycophenolate 36%](#) [Co-trimoxazole 32%](#) [Tacrolimus 21%](#) [Omeprazole 4%](#) [Chloramphenicol 0.5% eye drops 7%](#)

Out of all the options mycophenolate is the most likely medication to cause pancytopenia.

Other side effects to consider include:

- Taste disturbance
- Gingival hyperplasia
- Nausea and vomiting
- Constipation
- Gastrointestinal ulceration and bleeding.

## **Mycophenolate mofetil**

### Mode of action

- inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis
- as T and B cells are particularly dependent on this pathway it can reduce proliferation of immune cells

### Question 3 of 49

A 51-year-old man presents to the emergency department with a 2-week history of lumbar back pain. He has a background of asthma, hypertension and benign prostatic hypertrophy (BPH). He has no history of trauma. Apart from a recent exacerbation of asthma, he is otherwise well.

On examination, you find a man of large body habitus. He is able to mobilise with some discomfort. He is afebrile, with a heart rate of 75 beats per minute and blood pressure 120/82mmHg. He has some spinal tenderness at L4, and discomfort on extension of the spine. On neurological examination he has no muscle wasting or fasciculations. He has full power in all limbs and normal tone. Reflexes are symmetrical and plantars downgoing. Sensation is intact and he has normal rectal tone, with no saddle anaesthesia.

Blood tests show:

Hb 14.1 g/dl  
Platelets  $245 \times 10^9/l$   
WBC  $8.0 \times 10^9/l$

Na<sup>+</sup> 137 mmol/l  
K<sup>+</sup> 4.0 mmol/l  
Urea 5.1 mmol/l  
Creatinine 82 µmol/l

Bilirubin 14 µmol/l  
ALP 42 u/l  
ALT 17 u/l  
CRP 3 mg/L  
PSA 3.1ng/mL

What is the most likely diagnosis?

[Paget's disease6%](#)[Infective discitis11%](#)[Spinal metastases9%](#)[Vertebral compression fracture46%](#)[Lumbar radiculopathy27%](#)

This man has a crush fracture of the lumbar spine. He has had repeated courses of steroid treatment for his asthma, which has led to the development of osteoporosis. A plain X-ray would reveal the diagnosis. Paget's disease is unlikely given the normal ALP. Back pain due to metastases can be a presenting feature of prostate carcinoma. Although this man has BPH, his normal PSA and ALP make metastatic prostate cancer unlikely. He does not have neurological signs or symptoms suggestive of lumbar radiculopathy. Raised inflammatory markers would be expected in infective discitis.

Other side effects of prolonged corticosteroid use include:

- Peptic ulcer
- Skin thinning
- Mood and sleep disturbance
- Central obesity
- Myopathy
- Avascular necrosis of bone
- Cataracts

### **Osteoporosis: glucocorticoid-induced**

We know that one of the most important risk factors for osteoporosis is the use of corticosteroids. As these drugs are so widely used in clinical practice it is important we manage this risk appropriately.

The most widely followed guidelines are based around the 2002 Royal College of Physicians (RCP) 'Glucocorticoid-induced osteoporosis: A concise guide to prevention and treatment'.

The risk of osteoporosis is thought to rise significantly once a patient is taking the equivalent of prednisolone 7.5mg a day for 3 or more months. It is important to note that we should manage patients in an anticipatory, i.e. if it likely that the patient will have to take steroids for at least 3 months then we should start bone protection straight away, rather than waiting until 3 months has elapsed. A good example is a patient with newly diagnosed polymyalgia rheumatica. As it is very likely they will be on a significant dose of prednisolone for greater than 3 months bone protection should be commenced immediately.

### **Management of patients at risk of corticosteroid-induced osteoporosis**

The RCP guidelines essentially divide patients into two groups.

1. Patients over the age of 65 years or those who've previously had a fragility fracture should be offered bone protection.
2. Patients under the age of 65 years should be offered a bone density scan, with further management dependent:

<b>T score</b>	<b>Management</b>
Greater than 0	Reassure
Between 0 and -1.5	Repeat bone density scan in 1-3 years
Less than -1.5	Offer bone protection

The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

#### Question 4 of 49

A 62-year-old lady is seen in the rheumatology clinic. She was diagnosed with rheumatoid arthritis 16 years ago. Her symptoms were relatively well controlled with a combination of methotrexate 20mg once per week, folic acid 5mg once per week and azathioprine 100mg once per day until the last few months when she complained of increasing joint pain with stiffness. Since then her methotrexate dose was gradually titrated to the current dose of 25mg per week. She reported that her joints were less painful and stiff in the morning. Unfortunately, she was also complained of increasing tiredness with an increasing quantity of respiratory tract infections, requiring antibiotics twice in the last six months. She also noted that she bruised more easily of late.

Examination revealed a slender 62-year-old systemically well lady. She was haemodynamically normal and afebrile. Cardiovascular and respiratory examinations were unremarkable, and abdominal examination revealed a mass arising from the left upper quadrant. Clinical examination of her joints revealed no evidence of synovitis or swelling.

Routine blood investigations prior to attending clinic were as follows:

Hb	115 g/l
MCV	84 fl
Platelets	$82 \times 10^9/l$
WBC	$3.5 \times 10^9/l$
Neutrophils	$1.6 \times 10^9/l$
Lymphocytes	$1.0 \times 10^9/l$
Eosinophils	$0.9 \times 10^9/l$

Na<sup>+</sup> 141 mmol/l  
K<sup>+</sup> 3.9 mmol/l  
Urea 7.0 mmol/l  
Creatinine 81 µmol/l

Bilirubin 12 µmol/l  
ALP 99 u/l  
ALT 13 u/l  
Albumin 39 g/l

What is the single most likely cause of the clinical and haematological abnormalities?

[Myelodysplastic syndrome6%Chronic lymphocytic leukaemia4%Marrow aplasia secondary to drug therapy22%Felty's syndrome62%Myelodysplasia6%](#)

Felty's syndrome is a complication of Rheumatoid Arthritis (RA). It consists of a combination of rheumatoid arthritis, neutropaenia and splenomegaly, and tends to affect RA of longstanding duration. The main differential diagnosis is drug-induced marrow aplasia; however, this would not easily account for the presence of splenomegaly.

### **Rheumatoid arthritis: complications**

A wide variety of extra-articular complications occur in patients with rheumatoid arthritis (RA):

- respiratory: pulmonary fibrosis, pleural effusion, pulmonary nodules, bronchiolitis obliterans, methotrexate pneumonitis, pleurisy
- ocular: keratoconjunctivitis sicca (most common), episcleritis, scleritis, corneal ulceration, keratitis, steroid-induced cataracts, chloroquine retinopathy
- osteoporosis
- ischaemic heart disease: RA carries a similar risk to type 2 diabetes mellitus
- increased risk of infections
- depression

Less common

- Felty's syndrome (RA + splenomegaly + low white cell count)
- amyloidosis

- Question 5 of 49
- A 78-year-old man has a cervical spine film after falling down the stairs at his house. He has no history of musculoskeletal problems, including no neck or arm pain.

The cervical spine film is shown below:



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- What does the cervical spine film show?
- [Diffuse idiopathic skeletal hyperostosis40%](#)[Multiple myeloma6%](#)[Cervical rib9%](#)[Spondylosis of the cervical spine27%](#)[Ankylosing spondylitis17%](#)

- The cervical film shows ossification of the anterior longitudinal ligament only sparing the segments C2/3.

- 

- 

- **Diffuse idiopathic skeletal hyperostosis**

- 

Diffuse idiopathic skeletal hyperostosis (DISH) describes the relatively common finding of ossification at sites of tendinous and ligamentous insertion of the spine. It tends to be seen in elderly patients.

DISH is generally asymptomatic.



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- Ossification of the anterior longitudinal ligament only sparing the segments C2/3 consistent with DISH

#### Question 1 of 44

A 70-year-old man with rheumatoid arthritis presents for his monthly monitoring bloods because he is on methotrexate. He takes methotrexate 20mg once a week with folic Acid 5mg once weekly on a different day. He currently feels well in himself and his arthritis is well controlled. He does not drink alcohol or smoke. His monitoring blood tests come back as follows:



Hb	140 g/l	Na <sup>+</sup>	139 mmol/l	Bilirubin	14 µmol/l
Platelets	240 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.2 mmol/l	ALP	100 u/l
WBC	7 * 10 <sup>9</sup> /l	Urea	5 mmol/l	ALT	80 u/l
Neuts	4.5 * 10 <sup>9</sup> /l	Creatinine	87 µmol/l		

What is the correct course of action?

[Stop methotrexate4%Reduce methotrexate dose to 10mg once weekly12%Switch methotrexate to sulfasalazine4%Continue on current dose with repeat bloods in one month76%Stop methotrexate and urgent liver USS5%](#)

There is no need to stop methotrexate unless the alanine transaminase (ALT) or aspartate transaminase (AST) doubles according to the BSR guidelines. The patient should continue to have monthly blood test monitoring in the mean time.

See link below for full guidelines:

<http://www.rheumatology.org.uk/includes/documents/cmdocs/2009/d/diseasemodifyingantirheumaticdrugdmardtherapy.pdf>

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

### **Indications**

- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

### **Adverse effects**

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis

## Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

## Prescribing methotrexate

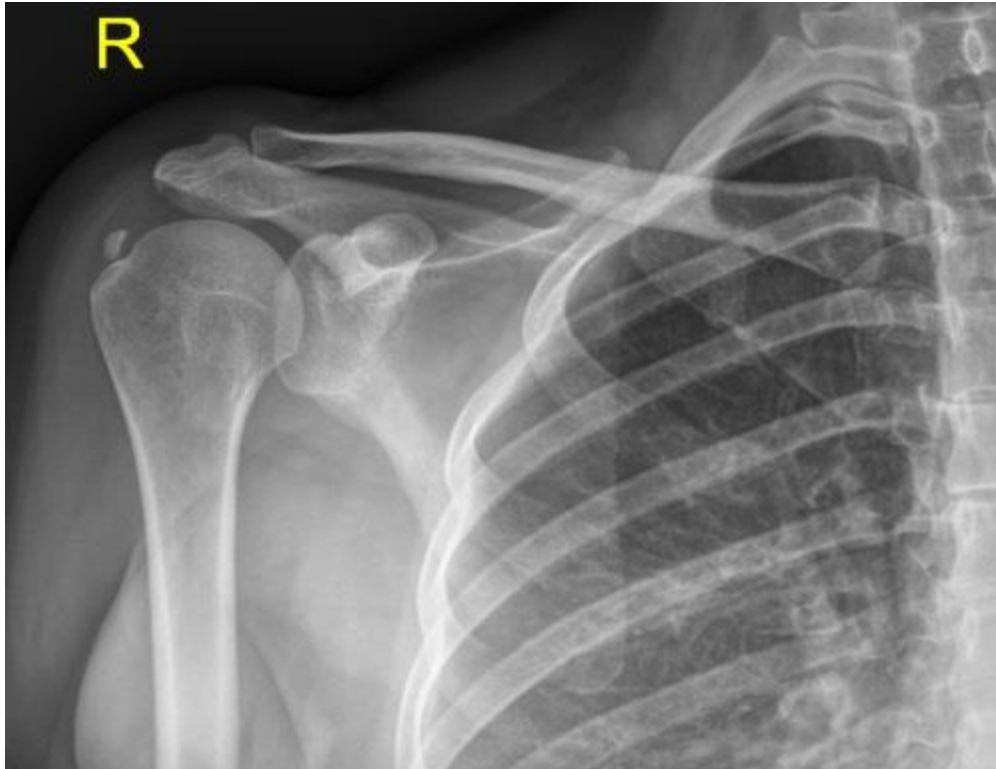
- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

## Question 2 of 44

A 48-year-old woman presents with progressively worsening pain in the right shoulder over the past few weeks. She is generally fit and well but smokes 20 cigarettes/day.

On examination there is diffuse mild tenderness over the lateral aspect of the right shoulder. The pain is recreated when abducting the should to around 70-80 degrees.

A shoulder x-ray is requested:



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What is the most likely diagnosis?

[Pancoast tumour](#)5% [Supraspinatus tendonitis](#)59% [Adhesive capsulitis](#)21% [Humeral head fracture](#)11% [Avascular necrosis](#)5%

The x-ray shows calcification of the supraspinatus tendon consistent with prolonged inflammation. On examination the patient exhibits the classical 'painful arc' associated with this condition.

## Shoulder problems

The table below summarises the key features of common shoulder problems:

Condition	Notes
<b>Adhesive capsulitis (frozen shoulder)</b>	Common in middle-age and diabetics Characterised by painful, stiff movement Limited movement in all directions, with loss of external rotation and abduction in about 50% of patients
<b>Supraspinatus tendonitis (Subacromial impingement, painful arc)</b>	Rotator cuff injury Painful arc of abduction between 60 and 120 degrees Tenderness over anterior acromion

### Question 3 of 44

A 65-year-old man was referred to rheumatology for advice regarding the management of his gout. The patient had suffered intermittent episodes of inflammation of the first metatarsophalangeal joint of both feet over the past ten years. The frequency of these episodes had been increasing, with 6 episodes in the past year. In addition, the patient's right knee had recently become inflamed with microscopy of synovial aspirate demonstrating needle shaped crystals with negative birefringence.

Colchicine and NSAIDs had been used effectively to provide symptomatic relief to the patient during an acute attack. Allopurinol had been previously trialled as prophylaxis at a dose of 200 mg daily, although was stopped after the patient's renal function was noted to have deteriorated after allopurinol was initiated. Lifestyle modifications have also been attempted.

Other medical problems included type 2 diabetes, hypertension, hypercholesterolaemia and chronic renal failure. Regular medications were ramipril, metformin and simvastatin.

On examination the patient was noted to be obese without evidence of current joint inflammation. Tophi were noted on examination of the patient's ears. Blood tests taken prior to clinic attendance are listed below.

Hb 16.5 g/dl  
Platelets  $150 \times 10^9/l$   
WBC  $8.6 \times 10^9/l$

Na<sup>+</sup> 137 mmol/l

K <sup>+</sup>	4.7 mmol/l
Urea	11.2 mmol/l
Creatinine	190 µmol/l
eGFR	45 ml/min
Calcium (adjusted)	2.3 mmol/l
Urate	395 µmol/l

What is the best strategy for gout prophylaxis in this patient?

[Prednisolone 10 mg daily10%Colchicine8%Febuxostat67%Naproxen3%Reduced dose allopurinol12%](#)

Urate lowering therapy is indicated in recurrent attacks of acute gout, although there are no firm guidelines as to when to initiate therapy. Target serum uric acid levels are usually taken as less than 360 micromol / L. Febuxostat is a non-purine xanthine oxidase inhibitor approved by NICE for use in individuals, such as this patient, who are intolerant of allopurinol or in whom allopurinol is contra-indicated.

Prednisolone, colchicine and naproxen are all used in the acute treatment of gout. Extended use of colchicine and NSAIDs can be considered to reduce the risk of gout relapse during the instigation of allopurinol therapy but have no role as prophylactic therapy in isolation.

Allopurinol can cause renal, hepatic and severe skin reactions (allopurinol hypersensitivity syndrome) and is best avoided in this patient given previous worsening of renal function with a relatively low dose of allopurinol.

Roddy E, Mallen C, Doherty M. Gout. BMJ 2013;347:5648.

## **Gout: management**

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 450 µmol/l)

### Acute management

- NSAIDs
- intra-articular steroid injection
- colchicine\* has a slower onset of action. The main side-effect is diarrhoea

- oral steroids may be considered if NSAIDs and colchicine are contraindicated. A dose of prednisolone 15mg/day is usually used
- if the patient is already taking allopurinol it should be continued

Allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of  $< 300 \mu\text{mol/l}$
- NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol\*\*

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

Other points

- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension
- calcium channel blockers also decrease uric acid levels, possibly by a renal vasodilatory effect
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels

\*inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

\*\*patients with Lesch-Nyhan syndrome often take allopurinol for life

#### Question 4 of 44

A 24-year-old who is known to have psoriasis presents with arthralgia. She has noticed that her knuckles have become swollen and her psoriasis has got much worse over the last four months. On examination, she has severe plaque psoriasis on her extensors and scalp leading to alopecia. Her metacarpophalangeal joints are clearly swollen and tender. She is currently on naproxen 500mg BD, paracetamol 1g TDS, topical steroids and calcipotriol. What medication would you add?

[Leflunomide7%Sulfasalazine13%Hydroxychloroquine14%Methotrexate59%Infliximab8%](#)

Methotrexate is very effective at improving psoriatic arthritis but in addition to this it also has a dramatic effect on skin disease to a much greater extent than the other disease modifying anti-rheumatic drugs (DMARDs) listed. Therefore it is the DMARD of choice in psoriatic arthritis. If there was a contraindication to methotrexate leflunomide would be used second line for peripheral psoriatic arthritis. You would only use infliximab or another anti-TNF drugs first line if the patient had a predominantly axial spondyloarthritis. This is according to the European League Against Rheumatism (EULAR) guidelines, please see the link:  
<http://ard.bmj.com/content/71/1/4.full>

Hydroxychloroquine can worsen skin disease and has little efficacy on psoriatic arthritis and is therefore not used routinely in the condition.

### **Psoriatic arthropathy**

Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions. Around 10-20% percent of patients with skin lesions develop an arthropathy with males and females being equally affected

#### Types\*

- rheumatoid-like polyarthritis: (30-40%, most common type)
- asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- sacroilitis
- DIP joint disease (10%)
- arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

## Management

- treat as rheumatoid arthritis
- but better prognosis



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Notice the nail changes on this image as well



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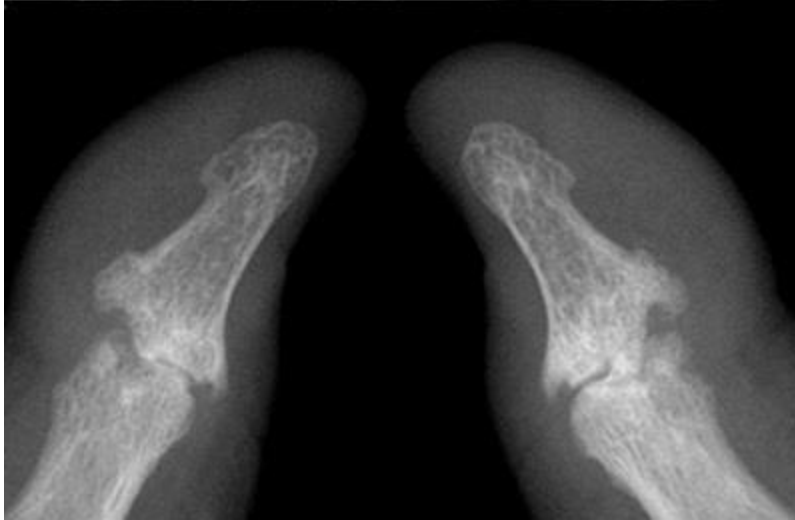
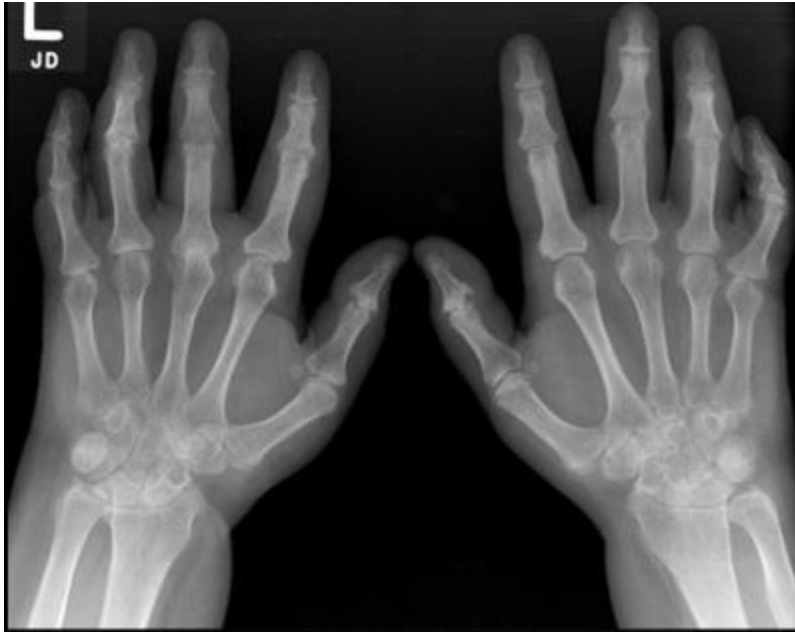






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X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.





This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progression towards a 'pencil-in-cup' changes.

\*Until recently it was thought asymmetrical oligoarthritis was the most common type, based on data from the original 1973 Moll and Wright paper. Please see the link for a comparison of more recent studies

#### Question 5 of 44

A 28-year-old woman presents to the gastroenterology clinic for review. She has been diagnosed with coeliac disease some 2 years earlier, and has been suffering from severe tiredness, muscle aches and proximal weakness for the past few months. On examination her blood pressure is 112/70 mmHg, pulse is 75 beats per minute and regular. You confirm proximal muscle weakness.

#### Investigations

Ca<sup>++</sup> 2.0 mmol/l

Alkaline phosphatase 275 IU/l

Which of the following is the most useful next investigation?

[CK12%](#)[Parathyroid hormone24%](#)[Vitamin D50%](#)[Muscle biopsy8%](#)[Electromyography5%](#)

Coeliac disease is known to interfere with absorption of fat soluble vitamins, including vitamin D, and the low calcium and elevated alkaline phosphatase, coupled with symptoms of proximal myopathy fits with a diagnosis of osteomalacia. Vitamin D levels are therefore the next investigation of choice.

CK and muscle biopsy are indicated for possible inflammatory myositis, and the limited proximal weakness seen here, coupled with low calcium is much more consistent with osteomalacia. Parathyroid hormone may be elevated, but this is secondary to low vitamin D and calcium. Electromyography is most useful for assessment of motor neuropathy, which doesn't fit with the painful proximal muscle weakness seen here.

## Osteomalacia

### Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion

### Types

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- renal failure
- drug induced e.g. anticonvulsants
- vitamin D resistant; inherited
- liver disease, e.g. cirrhosis

### Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

### Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase
- x-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (Looser's zones or pseudofractures)

### Treatment

- calcium with vitamin D tablets

### Question 1 of 39

A 28-year-old woman who is 20 weeks pregnant is referred to you by her GP. She has a 2-month history of arthralgia, myalgia, and fatigue. She had initially put this down to pregnancy but was finding it increasingly difficult to do her job as a health care assistant in a local nursing home.

She denied any shortness of breath, swallowing difficulties or alopecia.

She had asthma since childhood but was relatively well controlled on inhaled salbutamol as required and beclomethasone 400 micrograms twice daily.

She was a smoker of 10 cigarettes per day and had not drunk any alcohol since learning she was pregnant. She lives with her husband and 2-year-old son. Her mother has a history of rheumatoid arthritis.

Her observations show a blood pressure of 138/86 mmHg and a heart rate of 92 beats per minute. Urinalysis showed a trace of protein.

On examination there was tenderness of the 2nd and 3rd metacarpophalangeal (MCP) joints bilaterally and both wrists but no evidence of active synovitis. There are several painless mouth ulcers. You notice a few bruises on her arms but no other evidence of a rash. Her chest was clear and heart sounds were normal. Neurological examination was normal including full visual fields and eye movements.

Her bloods showed the following:

Haemoglobin	108 g/L
White Cell Count	$9.2 \times 10^9/\text{L}$
Platelets	$103 \times 10^9/\text{L}$
Neutrophils	$6.02 \times 10^9/\text{L}$
Lymphocytes	$0.80 \times 10^9/\text{L}$
Eosinophils	$0.90 \times 10^9/\text{L}$
ESR	29 mm/h

Urea	6.9 mmol/L
Creatinine	118 micromol/L
CRP	11 mg/L
Alkaline Phosphatase	87 iu/L

ALT	42 iu/L
-----	---------

Albumin	32 g/L
---------	--------

ANA	1: 320
dsDNA	24
Anti -Ro	Positive
Anti -La	Positive

Rheumatoid Factor	Positive
Anti CCP	Negative
Antiphospholipid antibody	negative

Given the most likely diagnosis, what complication needs to be discussed with her?

[Post partum haemorrhage6%](#)[Congenital heart block66%](#)[Deep vein thrombosis12%](#)[Pre-eclampsia10%](#)[Scleritis7%](#)

This question tests your knowledge of the diagnosis of Systemic Lupus Erythematosus (SLE). Diagnosis is based on the American College of Rheumatology (ACR) criteria written in 1982 and revised in 1997:

Four or more of the 11 criteria need to be fulfilled to be able to diagnose SLE. Note that while fatigue is a common feature it is not used in the diagnostic criteria. In this case, the criteria are oral ulcers + arthritis + positive dsDNA + the presence of ANA (while there is lymphopenia this is a single test result only)

In this case, there are sicca symptoms and Anti-Ro and -La antibodies suggesting an overlap with Sjogren's syndrome. Rheumatoid factor is positive in approximately 40% of SLE patients. The absence of anti-CCP should point you away from rheumatoid arthritis.

The point to make with this question is to test the candidate's knowledge of diagnosis of connective tissue diseases and their associated complications. Anti-Ro antibodies can cross the placenta and can lead to neonatal lupus and congenital heart block of the newborn, which can require pacing at birth. Miscarriage is another common complication of SLE. These can occur beyond the first trimester.

While postpartum haemorrhage, pre-eclampsia and deep vein thrombosis are complications of pregnancy that will need to be discussed, the presence of SLE does not increase the risk of either in this scenario. If the antiphospholipid antibody or lupus anticoagulant were positive then there is an increased risk of arterial or venous thrombosis, in which case you might consider anticoagulation but obviously not with warfarin in pregnancy.

## **Systemic lupus erythematosus: pregnancy**

### Overview

- risk of maternal autoantibodies crossing placenta
- leads to condition termed neonatal lupus erythematosus
- neonatal complications include congenital heart block

- strongly associated with anti-Ro (SSA) antibodies

#### Question 2 of 39

A 59-year-old lady comes to the blood pressure clinic with accelerated hypertension which isn't responding to lifestyle modifications.

The patient denies any headaches or blurred vision. However, she admits to a chronic cough and frequently passes pale, loose stools. She frequently gets cold hands and tells you they go red, white and then blue in the winter.

On examination, she is a thin lady with a blood pressure of 190/100 mmHg and a heart rate of 68 beats per minute. Although her nails are a normal colour she has tight, shiny skin over her hands. An ECG shows sinus rhythm.

Hb	106 g/l
Platelets	451 * 10 <sup>9</sup> /l
WBC	8.9 * 10 <sup>9</sup> /l
Na <sup>+</sup>	136 mmol/l
K <sup>+</sup>	4.9 mmol/l
Urea	7.1 mmol/l
Creatinine	174 µmol/l

Which of the following is the most appropriate initial therapy?

[Bisoprolol4%Candesartan6%Captopril58%Indapamide4%Amlodipine28%](#)

The patient describes Raynaud's phenomenon and mentions bowel and possibly lung involvement along with tight skin. This could point towards scleroderma. In this case, then, the raised creatinine and hypertension are suggestive of a scleroderma renal crisis. The first line treatment, in this case, is an ACE inhibitor.

Amlodipine would be the antihypertensive of choice if this were essential hypertension.

#### Systemic sclerosis

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

#### Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

#### Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

#### Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear





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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

Question 3 of 39

A 29-year-old woman is referred to Rheumatology clinic after experiencing all over pain throughout her body over the past two years. This has been associated with not feeling refreshed in the morning after a nights sleep and the patient finding difficulty in concentrating on her work in a call centre. She denied any history of skin rashes, photosensitivity, hair loss, swallowing difficulties or dry eyes and she had not lost any weight. Past medical history was significant for a previous diagnosis of mild depression treated with a course of cognitive behavioural therapy. There was no family history of connective tissue disease. The patient lived with her husband and two young children and reported some on-going concerns over the family finances. She smoked 10 cigarettes per day but rarely drank alcohol.

Initial review of the patient had demonstrated no evidence of inflammatory arthritis but showed the patient had significant muscular tenderness at multiple sites throughout the body.

Initial blood tests requested after clinic review had been unremarkable and included negative rheumatoid factor and negative anti-nuclear antibody. X-rays of the patient's hands and feet did not demonstrate any evidence of erosive arthropathy.

At a follow-up review of the patient with the above results, it was discussed that no evidence of inflammatory arthritis had been uncovered and that the patient's symptoms were most likely consistent with fibromyalgia. Given her previous experience with cognitive behavioural therapy, the patient was keen to adopt positive lifestyle strategies to reduce her symptoms rather than pharmacological treatment.

Which non-pharmacological treatment below has most evidence of effectiveness in fibromyalgia?

[Strength training14% Balneotherapy6% Aerobic exercise62% Electrotherapy4% Acupuncture14%](#)

Many non-pharmacological therapies for fibromyalgia have been tried although evidence for their effectiveness is limited. Aerobic exercise has the strongest evidence of benefit with a Cochrane review showing that regular aerobic exercise improved wellbeing, aerobic capacity, tenderness and pain compared with no exercise. Strength training has also been shown to have some benefit but with a lower quality of evidence than for aerobic exercise.

There is only weak evidence to support passive physical therapies such as electrotherapy or balneotherapy (hot spa treatments). Acupuncture is often used in fibromyalgia although evidence of long-term benefit is available.

Carnes D, Underwood M, Rahman A. Fibromyalgia. BMJ 2014;348:g474.

## **Fibromyalgia**

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

### **Epidemiology**

- women are 10 times more likely to be affected
- typically presents between 30-50 years old

### **Features**

- chronic pain: at multiple site, sometimes 'pain all over'
- lethargy
- sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which lists 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007 and also a BMJ review in 2014.

- explanation
- aerobic exercise: has the strongest evidence base
- cognitive behavioural therapy
- medication: pregabalin, duloxetine, amitriptyline

### **Question 4 of 39**

9. A 39 year old woman presents to her GP with symptoms of dysuria and increased urinary frequency for the past three days. She also complains of lower abdominal pain but has no overt signs of systemic sepsis. Examination is entirely normal aside from mild suprapubic pain. Urine dip correlates with a diagnosis of urinary tract infection with positive nitrites, leukocytes, blood and protein. The sample is sent for culture. The patients medical history is significant only for rheumatoid arthritis for which she takes methotrexate, folic acid, ibuprofen and omeprazole.

Which one of the following antibiotics is contraindicated in this patient?

[Co-amoxiclav5%Ciprofloxacin8%Cefpodoxime6%Nitrofurantoin14%Trimethoprim66%](#)

The concurrent use of methotrexate and trimethoprim containing antibiotics may cause bone marrow suppression and severe or fatal pancytopenia

Trimethoprim is a common bacteriostatic antibiotic used in the treatment of uncomplicated urinary tract infections. It is bacteriostatic rather than bactericidal in that it inhibits bacterial replication rather induces bacterial death. Replication inhibition is achieved by interfering with the generation of thymidine, an essential amino acid base in DNA, by inhibiting the action of the enzyme dihydrofolate reductase which is an essential component of the thymidine metabolic pathway, using folate as a primary substrate. Trimethoprim may also be combined with sulphonamide drugs such as sulphamethoxazole to create antibiotics such as co-trimoxazole; these drugs work synergistically by inhibiting alternative enzymes in the thymidine synthesis pathway.

Although trimethoprim is a relatively safe and effective drug in the treatment of urinary tract infections it does have some contraindications due to its mechanism of action. Due to its antagonism of folate metabolism, it should not be used in pregnancy, particularly the first trimester due to the risk of neural tube defects. Another effect of inhibiting folate metabolism is the impairment of metabolically active tissues such as bone marrow or cancerous cells. This effect is exploited in chemotherapy agents such as methotrexate. This drug also inhibits folate metabolism to prevent tumour growth; it can also be used in treating rheumatoid arthritis. Concomitant use of methotrexate and trimethoprim can lead to severe and potentially fatal bone marrow suppression with pancytopenia. This likelihood is increased if the trimethoprim is coupled with a sulphonamide drug, and also in the elderly.

All the other drugs listed above may be used in conjunction with folate inhibiting chemotherapeutic agents, although penicillin containing agents and quinolone antibiotics can cause a reduction in metabolism of methotrexate and the full blood count should be monitored in prolonged courses. Similarly methotrexate and nitrofurantoin used together can cause hepatotoxicity and liver function should be closely monitored. The safest choice of drug above is cefpodoxime, an oral third generation cephalosporin, which has no significant clinical interactions with the other drugs this patient is taking.

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

## Indications

- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

## Adverse effects

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis

## Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

## Prescribing methotrexate

- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

A 24-year-old woman attends rheumatology clinic after several occasions of shoulder dislocation from minimal trauma. She also notes she has previously had joints in her finger 'slip'. She has a long history of reflux disease and takes 20mg omeprazole OD.

On examination you note hyperelastic skin and a mid-systolic click on auscultation of the heart.

Which of the following signs would aid a diagnosis of Ehlers-Danlos syndrome?

Angioid streaks 36% Retinal hamartoma 17% Corneal whorls 18% Kayser–Fleischer rings 7% Blue sclerae 22%

Ehlers-Danlos syndrome: angioid retinal streaks is a feature

This woman has Ehlers-Danlos syndrome, a connective tissue disease that can result in hyperelasticity and multiple subluxations. There are numerous genetic variants, but most are due to mutations in collagen (COL1 & COL3 in particular) and can be inherited in an autosomal dominant pattern.

Angioid streaks are narrow lines radiating from the optic disc due to breaks in the weakened Bruch's membrane and are a common feature.

Retinal hamartomas are found in tuberous sclerosis and corneal whorls in Fabry disease. Kayser–Fleischer rings are a hallmark of copper deposition in Descemet's membrane in Wilson's disease and are best appreciated by slit-lamp examination.

Blue sclerae are found in osteogenesis imperfecta and are merely a function of seeing the underlying choroidal veins, beneath the translucent sclerae.

## **Ehler-Danlos syndrome**

Ehler-Danlos syndrome is an autosomal dominant connective tissue disorder that mostly affects type III collagen. This results in the tissue being more elastic than normal leading to joint hypermobility and increased elasticity of the skin.

### **Features and complications**

- elastic, fragile skin
- joint hypermobility: recurrent joint dislocation
- easy bruising
- aortic regurgitation, mitral valve prolapse and aortic dissection
- subarachnoid haemorrhage
- angioid retinal streaks

### Question 6 of 39

A 50-year-old man, presented with progressive shortness of breath and occasional dry cough of 4 weeks duration. He had underlying type 2 diabetes mellitus, hypertension and rheumatoid arthritis. He was a smoker with a smoking history of 15 pack years and a social drinker. His medications included metformin, enalapril and methotrexate which was started 6 weeks back along with folic acid supplementation.

On examination, his pulse rate was 100/min, blood pressure was 140/90 mmHg, respiratory rate was 20/min and was saturating 94% in room air. His chest revealed bibasal crackles on auscultation.

His blood counts were as follows-

Hb	150 g/l
Platelets	$150 \times 10^9/l$
WBC	$10 \times 10^9/l$
Eosinophils	$0.7 \times 10^9/sup/l$

CT chest showed patchy bilateral ground glassing with septal lines and few patchy consolidative changes.

What will be the appropriate next management?

[Cease methotrexate and start prednisolone 1mg/kg,45%](#)[Continue current treatment and add azithromycin7%](#)[Cease methotrexate and increase the dose of folic acid7%](#)[Cease methotrexate and evaluate for infections and cardiac failure37%](#)[Lung biopsy4%](#)

The most likely diagnosis in the above case was methotrexate induced lung injury. But atypical infections, cardiac failure can present in the same way especially when the patient has underlying risk factors. The ideal management would be to cease methotrexate and evaluate for infections and heart failure. A fibre optic bronchoscopy and bronchoalveolar lavage could be needed if the patient is not producing adequate sputum for cultures. Most of the cases of methotrexate induced lung injury respond to cessation of methotrexate alone. Steroids could be added in severe cases. Lung biopsy is rarely needed when the diagnosis is uncertain. While many adverse reactions to methotrexate, such as stomatitis, and myelosuppression, can be alleviated or prevented by the addition of supplemental folic or folinic acid (leucovorin), which selectively rescues normal cells from methotrexate toxicity without altering its therapeutic efficacy, repletion of folate stores does not reduce the risk for methotrexate induced pulmonary toxicity, suggesting that mechanisms other than intracellular folate depletion are involved in their genesis.

Reference:

- 1) Fishman's pulmonary disease and disorders-4th edition
- 2) Kremer JM, Alarcón GS, Weinblatt ME, et al. Clinical, laboratory, radiographic, and

histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. *Arthritis Rheum* 1997; 40:1829.

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

### Indications

- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

### Adverse effects

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis

### Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

### Prescribing methotrexate

- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'



- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

#### Question 7 of 39

A 53-year-old has just been diagnosed with rheumatoid arthritis whilst having a severe flare. She is started on methotrexate 15mg once weekly, folic acid 5mg once weekly, hydroxychloroquine 200mg BD, naproxen 250mg TDS and prednisolone 15mg OD. She returns one month later complaining of mouth ulcers. Bloods show the following:

Hb	142 g/l
Platelets	225 * 10 <sup>9</sup> /l
WBC	6 * 10 <sup>9</sup> /l
Na <sup>+</sup>	136 mmol/l
K <sup>+</sup>	4.2 mmol/l
Urea	4 mmol/l
Creatinine	95 µmol/l
Bilirubin	6 µmol/l
ALP	105 u/l
ALT	92 u/l

What is the most appropriate course of action?

[Admit for IV methylprednisolone](#)

[8%Stop methotrexate, hydroxychloroquine and naproxen4%Increase folic acid to two days a week21%Stop hydroxychloroquine and discuss with rheumatology20%Stop methotrexate and discuss with rheumatology47%](#)

According to BSR guidelines, if new oral ulceration starts whilst a patient is on methotrexate then it should be withheld initially and discussed with the specialist team.

In this patient, the alanine transaminase (ALT) is not two times the upper range of normal so that does not affect your decision. Often the folic acid is increased to six days a week (apart from the day of methotrexate) to mitigate side effects.

Hydroxychloroquine and naproxen are not associated with oral ulceration.

Full guidelines are found at the link below:

<http://www.rheumatology.org.uk/includes/documents/cmdocs/2009/d/diseasemodifyingantirheumaticdrugdmardtherapy.pdf>

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

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- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
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#### Question 8 of 39

A 35-year-old woman presents to rheumatology clinic with a 2-month history of symmetrical swelling of the ankles and fingers. She also complains of joint pain and stiffness. The stiffness is primarily worse in the early morning and eases with use. Apart from a recent sore throat, she is otherwise well. She has a family history of type 1 diabetes mellitus. She does not take any prescribed medication but has found herself relying on over-the-counter analgesics to get through the day.

On examination, she has bilateral swelling of the index, ring and middle fingers and bilateral ankle swelling. She has a full range of movement in the fingers, wrists and ankles. There is marked swelling and tenderness to palpation at the distal interphalangeal joints in the index, middle and ring fingers on both sides. There are no skin changes, but yellowing and pitting of the nails are noted.

Blood tests show:

Hb        11.1 g/dl  
 Platelets 305 \* 10<sup>9</sup>/l  
 WBC     7.8 \* 10<sup>9</sup>/l

Na<sup>+</sup>       141 mmol/l  
 K<sup>+</sup>       4.2 mmol/l  
 Urea      5.8 mmol/l  
 Creatinine 64 µmol/l

Bilirubin        13 µmol/l  
 ALP              83 u/l  
 ALT              15 u/l  
 ESR              50mm/hr

CRP 39 mg/L  
Rheumatoid factor negative

Hand X-ray shows mild erosion at the distal interphalangeal joints of the index, middle and ring fingers on both hands.

What is the diagnosis?

[Rheumatoid arthritis 11%](#) [Reiters syndrome 5%](#) [Ankylosing spondylitis 4%](#) [Yellow nail syndrome 15%](#) [Psoriatic arthritis 66%](#)

Although the patient does not have a psoriatic rash, she has classic symptoms of psoriatic arthritis. She has dactylitis and distal interphalangeal swelling, as well as ankle involvement. Nail signs are well-documented in psoriasis. The diagnosis is clinched by the negative rheumatoid factor and raised inflammatory markers. A slightly low haemoglobin is also a common feature of the disease. The pattern of joint involvement points more towards psoriatic arthritis than rheumatoid arthritis, in which the metacarpophalangeal joints and wrists are more commonly affected. Reiter's syndrome is a reactive arthritis that typically follows a gastrointestinal or venereal infection. Conjunctivitis and urethritis are seen alongside arthritis. Back pain would be expected to accompany ankylosing spondylitis. Yellow nail syndrome is a rare disorder of uncertain pathogenesis. It presents with nail discolouration, lymphoedema and pleural effusions.

Psoriatic arthritis can manifest in the absence of skin signs, particularly if the patient has a family history of psoriasis. The patient may develop a rash later or have signs limited to the nails.

## **Psoriatic arthropathy**

Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions. Around 10-20% percent of patients with skin lesions develop an arthropathy with males and females being equally affected

Types\*

- rheumatoid-like polyarthritis: (30-40%, most common type)
- asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- sacroilitis
- DIP joint disease (10%)
- arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

## Management

- treat as rheumatoid arthritis
- but better prognosis



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Notice the nail changes on this image as well



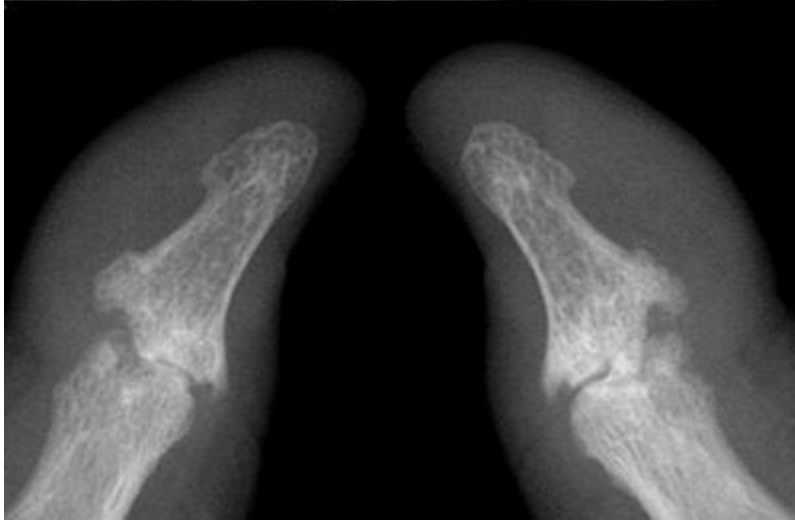
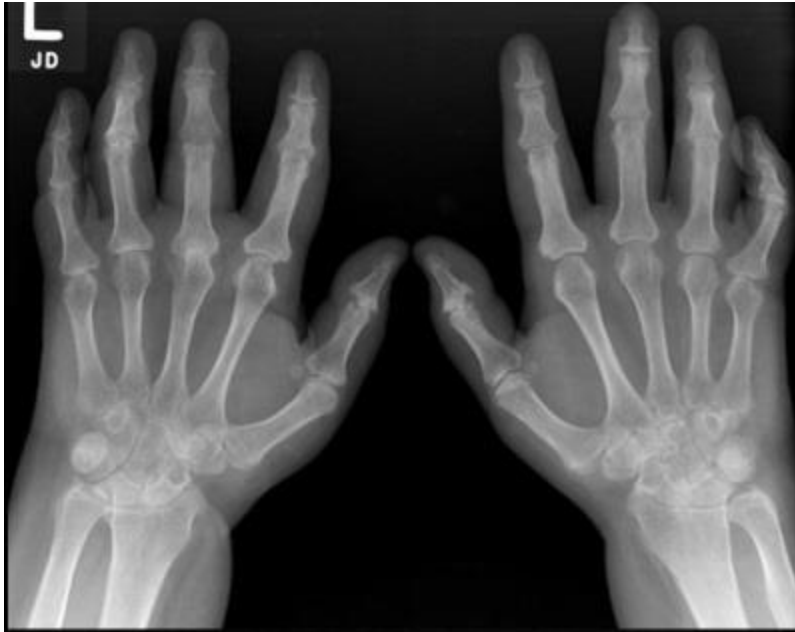
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X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.





This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progression towards a 'pencil-in-cup' changes.

\*Until recently it was thought asymmetrical oligoarthritis was the most common type, based on data from the original 1973 Moll and Wright paper. Please see the link for a comparison of more recent studies

#### Question 9 of 39

An 88-year-old female is admitted to hospital after recurrent mechanical falls. Her past medical history includes anterior resection for sigmoid carcinoma, type 2 diabetes mellitus and gout. Three days into her admission, she was treated for hospital-acquired pneumonia with three days of intravenous tazocin. One week into her admission, she developed a swollen inflamed 2nd MTP joint and colchicine was started. After becoming medically stable 10 days into admission and awaiting a package of care at home, nursing staff report diarrhoea, with type 7 stool up to 7 times a day. She has no laxatives prescribed. One set of stool cultures were sent within 15 minutes of the last episode, which have proved negative for *Clostridium difficile* toxin and antigen, MC+S and norovirus. What is the most likely cause of her diarrhoea?

[Clostridium difficile](#)11%[Norovirus](#)6%[Colchicine](#)71%[Recurrence of colon carcinoma](#)5%[Tazocin](#)7%

Colchicine is a classic cause of diarrhoea, particularly in the elderly and in higher doses, leading to the old adage of 'you run before you walk!' Antibiotics can induce diarrhoea without infection, particularly those acting on anaerobes<sup>1</sup>. It is unusual in this timeframe, having diarrhoea 4 days after the antibiotics finished. However, the most serious cause in this scenario is whether tazocin has resulted in pseudomembranous colitis, resulting in *Clostridium difficile* infection. In this case, negative samples for antigens and toxins are likely to be a true negative result. The main concern regards samples that were not transported to the lab promptly (within 2 hours), resulting in the breakdown of *Clostridium difficile* toxin, hence a false negative result. There is little to suggest cancer recurrence or an outbreak of norovirus.

1. Barbut F, Meynard L. Managing antibiotic associated diarrhoea. BMJ 2002; 324

#### Gout: management



Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 450  $\mu\text{mol/l}$ )

#### Acute management

- NSAIDs
- intra-articular steroid injection
- colchicine\* has a slower onset of action. The main side-effect is diarrhoea
- oral steroids may be considered if NSAIDs and colchicine are contraindicated. A dose of prednisolone 15mg/day is usually used
- if the patient is already taking allopurinol it should be continued

#### Allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300  $\mu\text{mol/l}$
- NSAID or colchicine cover should be used when starting allopurinol

#### Indications for allopurinol\*\*

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

#### Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

#### Other points

- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension

- calcium channel blockers also decrease uric acid levels, possibly by a renal vasodilatory effect
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels

\*inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

\*\*patients with Lesch-Nyhan syndrome often take allopurinol for life

#### Question 1 of 30

A 66-year-old Caucasian female presents with 3 week history of worsening headache and 2 day history of shortness of breath. She reports disturbed sleeping at night due to an inability to lie down, due to her shortness of breath. She has no known past medical history and drug history. On examination, you note bilateral splinter haemorrhages, 4 on the right and 2 on the left, with calcium deposits distally and black spots in the pulp of the fingers. Perioral skin puckering is also noted. Cardiovascular examination is unremarkable, chest examination reveals bilateral coarse inspiratory crackles. Neurological examination is unremarkable except fundoscopy revealing papilloedema, cotton wool spots and flame haemorrhages. The patient is afebrile, SpO<sub>2</sub> 95% on 2 litres, respiratory rate 24/min, blood pressure 195/115 mmHg, HR 90/min and regular. Chest x-ray demonstrates bilateral pleural effusion with bilateral alveolar shadowing. What is the most important immediate management?

[Oral amlodipine 6%](#) [Oral captopril 38%](#) [Intravenous labetalol 33%](#) [Oral high-dose prednisolone 16%](#) [Renal dialysis 7%](#)

This patient presents with signs of cutaneous manifestations of systemic sclerosis, grade 4 hypertensive retinopathy and heart failure. She is in scleroderma renal crisis (SRC), an emergency that if left untreated, is fatal. The optimal drug of choice is an ACE inhibitor, preferably captopril, which has been trialed with the greatest experience, but other ACEi are also likely to be beneficial. In a 15 year prospective cohort, one year survival increased from 15% to 76% with the use of ACEi against other anti-hypertensives<sup>1</sup>. Steroids should be strictly avoided in SRC, they increase the risk of SRC prior to the event and may exacerbate SRC in the acute setting. Renal dialysis may be required in patients who progress to end-stage renal failure despite ACEi treatments.

1. Steen VD, Costantino JP, Shapiro AP et al. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med. 1990;113(5):352

## **Systemic sclerosis**

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

### Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

### Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

### Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear



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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

## Question 2 of 30

A 40-year-old man is stable on warfarin therapy for the treatment of atrial fibrillation. Whilst on a stag party in Spain he develops scrotal pain and itching. Whilst in Spain, he is treated with a course of ciprofloxacin for a presumed urinary tract infection. Two weeks later he develops a hot, red, swollen and painful knee and both elbows become inflamed. On examination in the emergency department you identify localised tenderness of the knee and painful movement in all directions. The knee is red and hot. Both elbows are mildly warm, with painful movement on flexion and extension. His conjunctiva are also red. He is afebrile. Examination of his external genitalia is essentially normal however there is evidence of excoriation around the scrotum. What is the cause of his knee pain?

[Reactive arthritis 78%](#)[Still's disease4%](#)[Septic arthritis 5%](#)[Gout3%](#)[Haemarthrosis9%](#)

Reactive arthritis affects the joints, eyes and genitourinary/gastrointestinal system. It has been associated with gastrointestinal (GI) infections including Shigella, Salmonella, Campylobacter,

and other organisms, as well as with genitourinary (GU) infections (especially with Chlamydia trachomatis). The clinical triad commonly occurs 1-4 weeks following exposure.

Ciprofloxacin interacts with warfarin causing prolonged INR which is a risk factor for haemarthrosis, but the history of conjunctivitis and GU symptoms does not support this.

### **Reactive arthritis: features**

Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies. It encompasses Reiter's syndrome, a term which described a classic triad of urethritis, conjunctivitis and arthritis following a dysenteric illness during the Second World War. Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA).

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

#### **Features**

- typically develops within 4 weeks of initial infection - symptoms generally last around 4-6 months
- arthritis is typically an asymmetrical oligoarthritis of lower limbs
- dactylitis
- symptoms of urethritis
- eye: conjunctivitis (seen in 50%), anterior uveitis
- skin: circinate balanitis (painless vesicles on the coronal margin of the prepuce), keratoderma blenorrhagica (waxy yellow/brown papules on palms and soles)

Around 25% of patients have recurrent episodes whilst 10% of patients develop chronic disease

'Can't see, pee or climb a tree'



Keratoderma blennorrhagica

#### Question 3 of 30

A 55-year-old man is referred to rheumatology for management of severe tophaceous gout. The patient had been experiencing intermittent gout attacks over the previous few years, typically affecting the first metatarsophalangeal joints of both feet. However, during the last two months the patient had developed inflammation of multiple small joints of his hand preventing the patient from continuing his work as a train driver. A trial of Colchicine prescribed by the patient's General Practitioner had been discontinued after the patient experienced severe diarrhoea. Past medical history included an upper GI bleed secondary to a duodenal ulcer six months previously.

Examination demonstrated severe asymmetrical inflammation of multiple metacarpalphalangeal, distal interphalangeal and proximal interphalangeal joints across both hands. Yellow-white tophi were present across the inflamed joints. Blood tests taken prior to clinic attendance are listed below.

Hb        15.2 g/dl  
Platelets 265 \* 10<sup>9</sup>/l  
WBC     6.5 \* 10<sup>9</sup>/l

Na<sup>+</sup>       134 mmol/l  
K<sup>+</sup>       4.2 mmol/l  
Urea      9.5 mmol/l  
Creatinine 175 µmol/l

eGFR 62 ml/min  
Urate 370  $\mu$ mol/l

What is the best treatment for this patient's acute gout?

[Intra-articular steroid injection16% Naproxen9% Allopurinol7% Febuxostat21% Short course prednisolone47%](#)

The best option in this case is a short course of oral prednisolone (30 mg daily for five days). Two randomised controlled trials have shown this treatment to have a similar efficacy compared to NSAIDs. Intra-articular steroid injection is felt to be an effective treatment for acute gout affecting large joints, but is less appropriate for treatment of multiple small joints of the hands. Naproxen would be contra-indicated in this case due to the history of peptic ulceration and renal impairment.

Allopurinol and Febuxostat are both used to lower serum urate levels as part of gout prophylaxis and have no role in the treatment of an acute attack.

Roddy E, Mallen C, Doherty M. Gout. BMJ 2013;347:5648.

## **Gout: management**

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 450  $\mu$ mol/l)

### Acute management

- NSAIDs
- intra-articular steroid injection
- colchicine\* has a slower onset of action. The main side-effect is diarrhoea
- oral steroids may be considered if NSAIDs and colchicine are contraindicated. A dose of prednisolone 15mg/day is usually used
- if the patient is already taking allopurinol it should be continued

### Allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early



- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l
- NSAID or colchicine cover should be used when starting allopurinol

#### Indications for allopurinol\*\*

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

#### Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

#### Other points

- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension
- calcium channel blockers also decrease uric acid levels, possibly by a renal vasodilatory effect
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels

\*inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

\*\*patients with Lesch-Nyhan syndrome often take allopurinol for life

#### Question 4 of 30

A 45-year-old woman was referred to Rheumatology clinic after experiencing widespread aches and pains felt throughout her body. The pains were felt particularly in her arms and legs in addition to significant pain throughout the patient's spinal column. The patient could not recall a

precise onset of her symptoms but she felt they had been present for at least 12 months, possibly longer. In addition, the patient reported on-going feelings of tiredness and lethargy. Despite going to bed around 10 pm each evening, the patient reported waking in the morning still feeling exhausted. She denied any history of hot or tender joints, skin rashes, hair loss, swallowing difficulties or dry eyes. The patient's appetite was described as normal for her with no significant change in weight.

There was no previous past medical history and the patient took no regular medications except for a non-prescription multi-vitamin. Family history was remarkable for hypothyroidism affecting her mother and elder sister. The patient worked as an accountant and lived with her two teenage children. She had separated from her ex-husband 18 months previously.

The examination did not demonstrate any evidence of active synovitis of the hands or feet with no other inflamed or deformed joints. Palpation of the muscles of the upper arms and legs as well as the paraspinal muscles was exquisitely tender. Neurological examination of the arms and legs was unremarkable. The cardiovascular and respiratory examination was unremarkable with no skin rashes.

During clinic interaction, the patient appeared tired and stressed but had a good rapport and maintained good eye contact. She denied any significant low mood but was anxious that her symptoms represented a serious underlying illness.

Investigations requested following clinic are listed below.

Haemoglobin	129 g / L
White cell count	$7.2 \times 10^9/l$
Platelets	$332 \times 10^9/l$
Mean cell volume	87 fL
Sodium	140 mmol / L
Potassium	3.6 mmol / L
Urea	3.5 mmol / L
Creatinine	68 micromol / L
Erythrocyte sedimentation rate	11 mm / h
Rheumatoid factor	Negative
Anti-nuclear antigen	Weak positive
B12	324 pmol / L (reference 74-516)
Folate	30 nmol / L (reference 7-36)
Serum immunoglobulin	Normal electrophoresis strip
Thyroid stimulating hormone	0.9 microU / mL (reference 0.4-5.0)

X-rays of hands: some minor degenerative change in right index proximal interphalangeal joint but otherwise unremarkable with no boney erosion or deformity

What is the cause of the patient's pain?

[Fibromyalgia75%](#)[Systemic lupus erythematosus4%](#)[Chronic regional pain syndrome11%](#)[Generalised anxiety disorder5%](#)[Depression4%](#)

The patient has chronic widespread pain (>3 months) associated with lethargy, non-refreshing sleep and multiple tender points on palpation. Basic blood tests are essentially normal and there is no history or examination to suggest connective tissue disease or other pathology. This presentation is consistent with fibromyalgia, the diagnostic label used to describe chronic widespread pain associated with multiple muscular tender points or associated symptoms of fatigue, non-refreshing sleep or cognitive dysfunction.

Please note that many healthy individuals have weakly positive anti-nuclear antigen results and this does not imply a diagnosis of systemic lupus erythematosus in the absence of symptoms and signs of the disease. It may be that requesting immunological tests was inappropriate in this patient given the lack of clinical evidence of connective tissue disease.

Chronic regional pain syndrome is associated with persistent burning pain in one limb, usually after a minor injury. The brief mental state examination documented does not suggest evidence of significant depression or generalised anxiety.

Carnes D, Underwood M, Rahman A. Fibromyalgia. BMJ 2014;348:g474.

## **Fibromyalgia**

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

### **Epidemiology**

- women are 10 times more likely to be affected
- typically presents between 30-50 years old

### **Features**

- chronic pain: at multiple site, sometimes 'pain all over'
- lethargy
- sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which lists 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007 and also a BMJ review in 2014.

- explanation
- aerobic exercise: has the strongest evidence base
- cognitive behavioural therapy
- medication: pregabalin, duloxetine, amitriptyline

#### Question 2 of 25

A 6 year-old boy from Sierra Leone presents with a 1 week history of painful left arm. He is homozygous for sickle cell disease. On examination the child is pyrexial at 40.2°C and there is bony tenderness over the left humeral shaft. Investigations are:

Hb 7.1 g/dL

Blood culture Gram negative rods

X-ray left humerus: Osteomyelitis - destruction of bony cortex with periosteal reaction.

What is the most likely responsible pathogen?

[\*Escherichia coli\*11%Non-typhi \*Salmonella\*62%\*Pseudomonas aeruginosa\*8%\*Staphylococcus Aureus\*10%Parvovirus B1910%](#)

Blood and bone infections caused by non-typhi salmonella (NTS) are typically associated with malaria and homozygous sickle cell disease, especially in children. The reason for this perceived susceptibility is not fully understood - but it may be in part due to the haemolysis and subsequent iron availability to the bacteria, which is 'siderophilic' in nature.

*E.coli* and *P. aeruginosa* are not typically linked to sickle cell disease and *Staphylococcus aureus* is a gram positive coccus.

The haemoglobin level is normal for a child homozygous for sickle cell disease. Therefore

'aplastic anaemia' should not be considered and parvovirus can be ruled out. Parvovirus does not cause osteomyelitis.

## **Osteomyelitis**

Osteomyelitis describes an infection of the bone.

*Staph. aureus* is the most common cause except in patients with sickle-cell anaemia where *Salmonella* species predominate.

Predisposing conditions

- diabetes mellitus
- sickle cell anaemia
- intravenous drug user
- immunosuppression due to either medication or HIV
- alcohol excess

Investigations

- MRI is the imaging modality of choice, with a sensitivity of 90-100%

Management

- flucloxacillin for 6 weeks
- clindamycin if penicillin-allergic

Question 4 of 25

A 28-year-old woman with systemic lupus erythematosus attends the pre-conception clinic. She would like some advice regarding her medications prior to getting pregnant. She has never been pregnant before and her lupus has been stable on her current medications: mycophenolate and hydroxychloroquine for over 12 months. She also has asthma, which is well controlled with beclomethasone and salbutamol inhalers, and she takes regular omeprazole for gastro-oesophageal reflux.

What is the most appropriate medication amendment?

[Half omeprazole dose5%Stop beclomethasone inhaler5%Stop hydroxychloroquine18%Add ramipril 1.25mg3%Change mycophenolate to azathioprine69%](#)

Unlike the majority of autoimmune conditions, pregnancy increases the likelihood of a lupus flare. It is essential that a patient's lupus is well controlled and quiescent for at least six months prior to pregnancy. Given that mycophenolate is teratogenic in pregnancy, it must be stopped. It is common practice to change to azathioprine, which has been shown to be safe in pregnancy - but still used with caution! However knowledge of common medications used/not used in pregnancy should also lead the candidate to this option.

There is no need to stop the beclomethasone or hydroxychloroquine, as they are both safe in pregnancy. Omeprazole is also safe in pregnancy and the dose does not need to be changed. ACE inhibitors are contraindicated in pregnancy and must be stopped/changed to another agent.

## **Systemic lupus erythematosus: management**

### Basics

- NSAIDs
- sun-block

### Hydroxychloroquine

- useful for skin disease

If internal organ involvement e.g. renal, neuro, eye then consider prednisolone, cyclophosphamide

### Question 5 of 25

A 20-year-old male presents with a 4-day history of joint pain in both his wrists, left 2nd metacarpal-phalangeal (MCP) joint and right knee; blood in his urine and a new rash on his cheeks, which particularly bothers him. He also complains of chest pain of non-specific nature, onset about one week ago. On examination, you note bilateral swollen MCP joints, a

hyperpigmented, raised erythematous rash on both cheeks. Neurological examination reveals a mild distal tremor at rest and activity, with bilateral KayserFleischer rings. He was diagnosed with Wilsons disease aged 18 years old and has no other past medical history. He is currently a research assistant and lives alone. His medications include ibuprofen as required, penicillamine started on diagnosis 2 years ago and he states he has been buying zinc supplements over the counter after reading in a journal that it may be helpful for his condition. Urine dip demonstrates 3+ blood, 1+ protein, no leucocytes or nitrites. Which blood test is most likely to be diagnostic of his most recent admission?

[Serum zinc7%Urinary zinc7%Anti-histone antibody63%Anti-C1q antibody6%Anti-double-stranded DNA antibody \(dsDNA\)16%](#)

The patient describes haematuria, a new erythematous rash on sun-exposed regions and arthritis, on a background of previous penicillamine use: this is consistent with drug-induced lupus erythematosus (DLE). A number of medications are known to induce DLE, including penicillamine, procainamide, minocycline, hydralazine and a number of anti-epileptics. There is no specific diagnostic test for DLE: a combination of a drug known to induce DLE, the presence of ANA and resolution of symptoms on offending drug withdrawal. However, it is known that anti-histone antibodies are particularly sensitive to DLE, positive in up to 95% of DLE patients. Anti-C1q antibody can be present but is particularly predictive of lupus nephritis later in the disease. Unlike systemic lupus erythematosus (SLE), anti-dsDNA is often not present in DLE.

The patient's symptoms are not consistent with that of zinc poisoning, classically presenting with abdominal pain, vomiting and diarrhoea. The treatment of Wilsons disease is initially involves a copper-chelating agent, either penicillamine or trientine. Zinc is generally not used unless the patient is intolerant of either. Liver transplantation is also considered for those presenting in acute liver failure only.

## **Drug-induced lupus**

In drug-induced lupus not all the typical features of systemic lupus erythematosus are seen, with renal and nervous system involvement being unusual. It usually resolves on stopping the drug.

### **Features**

- arthralgia
- myalgia
- skin (e.g. malar rash) and pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, dsDNA negative
- anti-histone antibodies are found in 80-90%
- anti-Ro, anti-Smith positive in around 5%



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A woman with drug-induced lupus

Most common causes

- procainamide
- hydralazine

Less common causes

- isoniazid
- minocycline
- phenytoin

Question 6 of 25

A 77-year-old lady is reviewed in the Rheumatology Clinic with a 4-week history of malaise and bilateral hip pain.

The pain is poorly localised and affects the anterior and posterior aspects of the pelvis as well as the upper thighs. It is typically worse in the mornings and associated with feelings of stiffness that take several hours to improve.



She also reports the recent onset of a right-sided headache, which is constant and has been present for the past 2 weeks. 24 hours ago, she developed an episode of transient visual darkening although she is unable to recall which eye was affected.

Her past medical history is remarkable for hypertension and hypothyroidism. Her regular medications include amlodipine 5mg once daily and levothyroxine 75 micrograms once daily.

On examination, her visual acuity is 6/9 in both eyes. Her temperature is 37.3°C, her pulse is 73bpm and her blood pressure is 143/81mmHg. Neurological examination reveals no focal abnormality although the pulsation of her right temporal artery is difficult to feel.

Her blood results are as follows:

Hb	124 g/l	Na <sup>+</sup>	141 mmol/l
Platelets	444 * 10 <sup>9</sup> /l	K <sup>+</sup>	3.9 mmol/l
WBC	11.2 * 10 <sup>9</sup> /l	Urea	4.3 mmol/l
Neuts	8.1 * 10 <sup>9</sup> /l	Creatinine	78 µmol/l
Lymphs	2.3 * 10 <sup>9</sup> /l	CRP	102 mg/l
Eosin	0.02 * 10 <sup>9</sup> /l		

A temporal artery biopsy is performed and a 0.8cm sample is obtained. It is reported as being 'negative for giant cell arteritis (GCA)'.

What is the most appropriate treatment strategy?

[IV methylprednisolone 1 gram once daily33% Prednisolone 15mg once daily9% Amitriptyline 10mg once daily3% Explanation, reassurance and referral to physiotherapy for graded aerobic exercise5% Prednisolone 60mg once daily50%](#)

This lady's presentation is consistent with GCA. The picture is complicated by additional features of polymyalgia rheumatica (PMR) although it is important to bear in mind that the two often occur together in clinical practice.

A normal temporal artery biopsy does not rule out GCA due to the possibility of skip lesions giving rise to a false negative result. 7-44% of patients with GCA will have a negative temporal artery biopsy and such falsely reassuring results are more likely to occur when shorter arterial specimens are obtained. For this reason, the British Society for Rheumatology (BSR) recommends that biopsy specimens should no less than 1cm in length.

Transient visual loss can herald the onset of permanent blindness and the BSR recommend that these patients receive IV methylprednisolone 500-1000mg daily for 3 days.

Those with established visual loss or uncomplicated GCA should receive 60mg prednisolone daily.

Prednisolone 15mg daily is the treatment for isolated PMR and would not be appropriate in this case. The remaining options are treatments for fibromyalgia and are therefore incorrect.

## **Temporal arteritis**

Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

### **Features**

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%)
- visual disturbances secondary to anterior ischemic optic neuropathy
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also lethargy, depression, low-grade fever, anorexia, night sweats

### **Investigations**

- raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- temporal artery biopsy: skip lesions may be present
- note creatine kinase and EMG normal

### **Treatment**

- high-dose prednisolone - there should be a dramatic response, if not the diagnosis should be reconsidered
- urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible

Question 1 of 19

A 67-year-old female presented to the accident and emergency department with severe headache and shortness of breath for the last six hours followed by seizures which occurred twice during the last hour.

The patient is a known case of diffuse cutaneous systemic sclerosis diagnosed two years ago and she is on steroids and cyclophosphamide.

On examination, she looks ill, agitated and dyspnoeic. Her pulse rate is 100 beats per minute, regular and her blood pressure is 220/110 mmHg.

Her JVP is raised, there is a gallop rhythm and bilateral basal crackles. There is lower limb oedema and brisk reflexes.

Fundoscopy showed grade 3 hypertensive retinopathy.

Investigations done two weeks previously showed:

Serum sodium 140 mmol/L

Serum potassium 5.7 mmol/L

Serum urea 17 mmol/L

Serum creatinine 250 mol/L

Urinalysis protein ++, blood ++

What is the most appropriate immediate treatment to lower her blood pressure?

[IV sodium nitroprusside 17%](#)[IV labetalol 22%](#)[Oral ACE inhibitor 46%](#)[IV hydralazine 7%](#)[Nitrate infusion 8%](#)

This patient has developed scleroderma renal crisis which presents as malignant hypertension, heart failure and rapid deterioration of renal function progressing to acute renal failure.

This hypertensive emergency should be managed with gradual reduction of blood pressure at a rate of 10-15 mmHg per day with an oral ACE inhibitor as the pathology of scleroderma renal crisis is vasospasm.

IV sodium nitroprusside and IV labetalol should be avoided as they lead to sudden reduction of blood pressure and renal hypoperfusion that leads to acute tubular necrosis, making the already deranged renal function even worse.

Indeed, this patient requires ICU admission for management of her heart failure and acute renal failure.

## **Systemic sclerosis**

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

### Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

### Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

### Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear



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## Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

## Question 1 of 18

A 37-year-old woman presents with left-sided pain shoulder pain. This has been present for around 6 months and is described variably as a 'toothache' or an 'electric shock' sensation which extends from her neck to the elbow.

On examination there is reduced power when abducting the left shoulder and reduced sensation to light touch just inferior to the deltoid muscle. The biceps reflex on the left side is absent. Pain and temperature sensation are normal in the left arm. Examination of the right arm is normal.

An MRI neck is requested:



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What is the most likely diagnosis?

[Bony metastases](#)6% [Brown-Sequard syndrome](#)7% [Arnold-Chiari malformation](#)11% [Syringomyelia](#)23% [Cervical disc prolapse](#)53%

This patient has signs consistent with a C5/6 myelopathy. Note the very large extruded disc at C5/6. There is also fusion of C2 and C3 with adjacent segment degeneration and cord volume loss suggesting myelomalacia.

## Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury Humeral neck fracture/dislocation Results in flattened deltoid
Axillary nerve (C5,C6)	Shoulder abduction (deltoid muscle)	Inferior region of the deltoid muscle	Humeral midshaft fracture Palsy results in wrist drop
Radial nerve (C5-C8)	Extension (forearm, wrist, fingers, thumb)  LOAF* muscles  Features depend on the site of the lesion:	Small area between the dorsal aspect of the 1st and 2nd metacarpals	
Median nerve (C6, C8, T1)	<ul style="list-style-type: none"> <li>wrist: paralysis of thenar muscles, opponens pollicis</li> <li>elbow: loss of pronation of forearm and weak wrist flexion</li> </ul>	Palmar aspect of lateral 3½ fingers	Wrist lesion → carpal tunnel syndrome
Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF*  Wrist flexion	Medial 1½ fingers	Medial epicondyle fracture Damage may result in a 'claw hand' Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy
Long thoracic nerve (C5-C7)	Serratus anterior		Damage results in a winged scapula



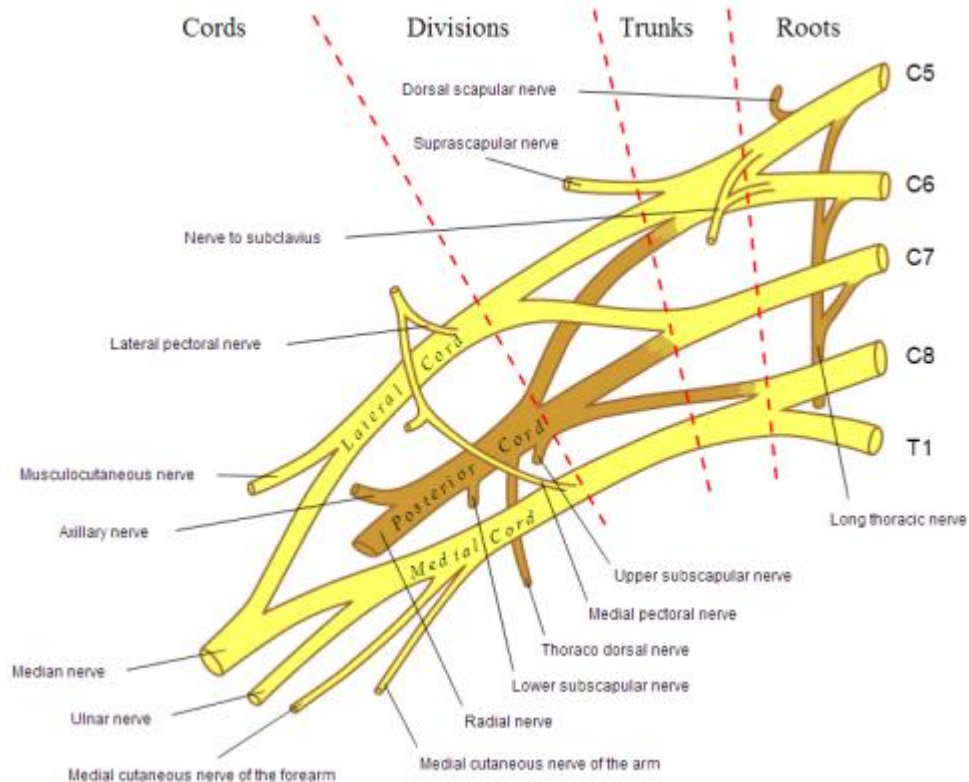


Diagram of the brachial plexus

### Erb-Duchenne palsy ('waiter's tip')

- due to damage of the upper trunk of the brachial plexus (C5,C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

### Klumpke injury

- due to damage of the lower trunk of the brachial plexus (C8, T1)
- as above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand
- associated with Horner's syndrome

### \*LOAF muscles

- Lateral two lumbricals
- Opponens pollicis
- Abductor pollicis brevis

- Flexor pollicis brevis

#### Question 2 of 18

A 40-year-old woman was diagnosed with fibromyalgia 6 months previously following review in the Rheumatology outpatient clinic. She was subsequently discharged from the clinic with a recommendation for a trial of pregabalin therapy. The patient has now returned to her General Practitioner to report on-going symptoms of severe widespread body pain, severe fatigue and difficulty in concentrating on daily activities. The patient did not feel that starting pregabalin 6 months previously had offered any improvement in her symptoms. In fact, her symptoms had been causing more problems and she had recently been unable to attend her work as a teaching assistant.

The patient's past medical history included a duodenal ulcer five years previously, induced by the combination of non-steroidal anti-inflammatory drug use and alcohol consumption. She also had a previous diagnosis of irritable bowel disease and had a tendency to become severely constipated. There were no known allergies to medications. The patient lived alone and in addition to her teaching assistant job was her elderly mother's primary carer.

On assessment by her General Practitioner, there was no evidence of inflammatory arthritis but multiple tender spots were demonstrated across the patient's body. The patient was clearly distressed and frustrated with her on-going symptoms and had concerns about her ability to continue in paid employment. The patient's affect was otherwise unremarkable with a good rapport maintained throughout. She denied any symptoms of low mood or thoughts of self-harm.

Following further discussion, the patient was keen to try a further pharmacological therapy as treatment for her fibromyalgia symptoms. She was reluctant to engage with suggested psychological therapies.

What is appropriate next line pharmacological treatment for the patient's fibromyalgia?

[Continue pregabalin, start duloxetine14%](#)[Continue pregabalin, start ibuprofen as required5%](#)[Stop pregabalin, start duloxetine37%](#)[Stop pregabalin, start amitriptyline33%](#)[Continue pregabalin, start fluoxetine12%](#)

The evidence base for pharmacological treatment of fibromyalgia includes many trials with small participant numbers and short follow-up periods. In addition, many trials have exclusion criteria (such as co-morbid psychiatric illness or chronic physical illness) that make generalisation to patients seen in clinical practice difficult.

Recent network meta-analysis has demonstrated that once trials with fewer than 50 participants are excluded then there is only evidence of effectiveness of duloxetine and pregabalin to improve pain and quality of life. Current recommendation is to use an agent at an effective dose for at

least four weeks then assess response. If no response obtained then initial treatment should be held before a new agent is started, for example stopping pregabalin before a trial of duloxetine as in this case.

Using ibuprofen or amitriptyline would likely be inappropriate for this patient given the previous history of peptic ulceration and constipation.

Carnes D, Underwood M, Rahman A. Fibromyalgia. BMJ 2014;348:g474.

## **Fibromyalgia**

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

### **Epidemiology**

- women are 10 times more likely to be affected
- typically presents between 30-50 years old

### **Features**

- chronic pain: at multiple site, sometimes 'pain all over'
- lethargy
- sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which lists 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007 and also a BMJ review in 2014.

- explanation
- aerobic exercise: has the strongest evidence base
- cognitive behavioural therapy
- medication: pregabalin, duloxetine, amitriptyline

### Question 3 of 18

A 38-year-old Armenian visitor presents with 3 day history of pyrexia, shortness of breath, chest pain and abdominal pain, associated with temperature of 38.5 degrees. She has no other known past medical history and reports at least 2 other episodes of similar pain, both times spontaneously resolving without treatment or diagnosis. On examination, she has a pleural rub and a swollen, tender left 3rd metacarpal-phalangeal joint. Her mother has recently been admitted for similar symptoms last month. Her blood tests are as follow:

Hb 14.5 g/dl  
Platelets  $560 \times 10^9/l$   
WBC  $17.8 \times 10^9/l$

Na<sup>+</sup> 143 mmol/l  
K<sup>+</sup> 4.6 mmol/l  
Urea 5.2 mmol/l  
Creatinine 78  $\mu$ mol/l  
CRP 78 mg/l

A chest radiograph demonstrates mild bilateral pleural effusions with no significant focus of consolidation, her Mantoux test is negative. Urine dip is negative, urine MC+S grows no organisms, urinary porphobilinogen is negative. A rheumatology review was requested regarding the synovitis and colchicine prescribed. She responds well with resolution of all symptoms within 24 hours. An infectious diseases opinion and induced sputum is awaited. What is the most likely diagnosis?

[Tuberculosis4%Acute intermittent porphyria \(AIP\)7%Coxsackie B virus infection7%Familial mediterranean fever74%Systemic lupus erythematosus \(SLE\)8%](#)

The patient is of Mediterranean descent is experiencing an acute attack of abdominal pain, chest pain, synovitis and pyrexia with an acute phase response. There appears to be a previous history of similar symptoms and a possible genetic element. Familial Mediterranean fever would fit with all these symptoms, with almost all patients presenting with abdominal pain, pleuritis and synovitis, associated with fever greater than 38 degrees. The main differentials in this case are with SLE and AIP: during an acute event, urinary porphobilinogen is likely positive in AIP. The distinguishing feature against SLE is the resolution of symptoms with colchicine, which is a key diagnostic feature<sup>1</sup>.

1. Livneh A, Langevitz P, Zemer D et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum.* 1997;40(10):1879

## **Familial Mediterranean Fever**

Familial Mediterranean Fever (FMF, also known as recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is more common in people of Turkish, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- pyrexia
- abdominal pain (due to peritonitis)
- pleurisy
- pericarditis
- arthritis
- erysipeloid rash on lower limbs

Management

- colchicine may help

Question 4 of 18

A 68-year-old lady attends for review in the oncology clinic. She has advanced oestrogen receptor positive, HER2 negative breast cancer, with metastasis to her ribs, thoracic vertebrae and right humerus. She previously underwent right mastectomy and first line chemotherapy but has declined further chemotherapy.

She has had back and rib pain which was improved by external beam radiotherapy. She was started on alendronate to help prevent pathological fractures but has since suffered nausea, severe acid reflux and epigastric discomfort not helped by a proton pump inhibitor. Her alendronate was stopped and risedronate was trialled but resulted in similar effects and so was also discontinued.

What is the most appropriate medication to prescribe this lady to help prevent skeletal related events?

[Denosumab61%Lapatinib3%Letrozole7%Strontium20%Trastuzumab9%](#)

This lady has bone metastases so is at risk of pathological fracture. The first choice agent would

be a bisphosphonate such as alendronate. However, this lady is unable to take bisphosphonates due to oesophageal irritation and nausea are common side effects.

Denosumab is a monoclonal antibody which binds to and inhibits RANKL on the surface of osteoclasts, preventing the break down of bone. It is approved by NICE for women with osteoporosis or with advanced breast cancer and bone metastases, who have been intolerant to bisphosphonates.

Strontium ranelate is recommended for primary prevention of osteoporotic fractures in at risk women who have been intolerant of bisphosphonates. However, it has not been shown to reduce skeletal related events in bone metastases.

Lapatinib is a tyrosine kinase inhibitor of the HER2 and epidermal growth factor receptors and is part therapy to treat HER2 positive breast cancer.

Letrozole is an aromatase inhibitor used to treat oestrogen receptor positive breast cancer. Although it is generally effective against these types of cancer, it has not been shown in trials to reduce skeletal related events in patients with this cancer type.

Trastuzumab is a monoclonal antibody against the HER2 receptor and is part of therapy to treat HER2 positive breast cancer.

#### References:

National Institute for Health and Care Excellence. Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours. NICE technology appraisal guidance [TA265] (2012)

National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal guidance 160 (2011)

## **Denosumab**

Denosumab is a relatively new treatment for osteoporosis. It is a human monoclonal antibody that inhibits osteoclast formation, function and survival. Remember that osteoblasts build bone, osteoclasts eat bone. It is given as a subcutaneous injection, at a dose of 60mg, every 6 months.

A larger dose of denosumab (120mg) may also be given every 4 weeks for the prevention of skeletal-related events (i.e. pathological fractures) in adults with bone metastases from solid tumours. For example, you may have noticed some of your breast cancer patients have been prescribed denosumab.

## **Where does it fit in the management of osteoporosis?**

Oral bisphosphonates are still given first-line, with oral alendronate being the first-line treatment. If alendronate is not tolerated then NICE recommend using an alternative bisphosphonate - either risedronate or etidronate. Following this the advice becomes more complicated with the next-line medications only being started if certain T score and other risk factor criteria being met. Raloxifene and strontium ranelate were recommended as next-line drugs in the NICE criteria but following recent safety concerns regarding strontium ranelate it is likely there will be an increasing role for denosumab.

NICE published a technology appraisal looking at the role of denosumab in 2010. A link is provided.

## **What are the known side-effects of denosumab?**

Denosumab is generally well tolerated. Dyspnoea and diarrhoea are generally considered the two most common side effects, occurring in around 1 in 10 patients. Other less common side effects include hypocalcaemia and upper respiratory tract infections.

## **What does the Drug Safety Update add?**

Cases of atypical femoral fractures have been noted in patients taking denosumab. Doctors are advised to look out for patients complaining of unusual thigh, hip or groin pain.

Question 5 of 18

An 18 year-old girl with neuropsychiatric Wilsons disease is commenced on chelation therapy.

One month later she presents with fatigue, generalised arthralgia, and an erythematous rash affecting the face, back of the neck, shoulders, and arms.

Which test is most specific for the suspected diagnosis?

[Anti-centromere antibodies5% Anti-Scl70 antibodies6% Anti-mitochondrial antibodies5% Anti-histone antibodies72% Anti-dsDNA antibodies12%](#)

This is drug-induced lupus as a result of penicillamine chelation therapy.

Anti-histone antibodies are specific for drug-induced lupus.

Other unusual side-effects of penicillamine include membranous glomerulonephritis and a myasthenia-like syndrome.

Other causes of drug-induced lupus include procainamide, minocycline, hydralazine, and

isoniazid.

Anti-centromere antibodies are found in limited systemic sclerosis.

Anti-Scl70 antibodies are found in diffuse systemic sclerosis.

Anti-mitochondrial antibodies are specific for primary biliary cirrhosis.

Anti-dsDNA antibodies are specific for systemic lupus erythematosus.

### **Drug-induced lupus**

In drug-induced lupus not all the typical features of systemic lupus erythematosus are seen, with renal and nervous system involvement being unusual. It usually resolves on stopping the drug.

#### **Features**

- arthralgia
- myalgia
- skin (e.g. malar rash) and pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, dsDNA negative
- anti-histone antibodies are found in 80-90%
- anti-Ro, anti-Smith positive in around 5%







## A woman with drug-induced lupus

### Most common causes

- procainamide
- hydralazine

### Less common causes

- isoniazid
- minocycline
- phenytoin

### Question 1 of 13

A 70-year-old male presents with a 3-month history of left foot drop. He complains of having to lift his thighs higher than normal to accommodate this pathology. On examination, he has a high stepping gait. Power is normal in all movements except left ankle dorsiflexion (2/5) and eversion (2/5). Ankle inversion is intact (5/5), ankle jerks are present and plantars are downgoing. He reports reduced sensation on the dorsum of his foot. What is the most likely diagnosis?

[L5 radiculopathy14%](#)[Common peroneal palsy73%](#)[Functional neurology4%](#)[Sciatic nerve compression5%](#)[Lumbar plexopathy4%](#)

The differential diagnosis of foot drop is a MRCP favourite. In this case, a number of features favour a common peroneal nerve palsy instead of a L5 radiculopathy: common peroneal nerve palsy patients normally have an intact ankle inversion and flexion of the big toe. Sensory loss is usually around the lateral aspect of the lower leg and the dorsum of the foot while L5 appears as a thin strip down the middle of the anterior lower limb, usually not affect the lateral lower leg. Ankle jerks are present in both, as the tibial nerve is branched from S1 and the sciatic nerve. There is little to suggest the involvement of multiple lumbar levels in this scenario. The most common causes of common peroneal nerve palsy are trauma or compression at the fibula head, classically by tight plaster casts.

## Common peroneal nerve lesion

The sciatic nerve divides into the tibial and common peroneal nerves. Injury often occurs at the neck of the fibula

The most characteristic feature of a common peroneal nerve lesion is foot drop

Other features include:

- weakness of foot dorsiflexion
- weakness of foot eversion
- weakness of extensor hallucis longus
- sensory loss over the dorsum of the foot and the lower lateral part of the leg
- wasting of the anterior tibial and peroneal muscles

Question 2 of 13

A 79-year-old woman complains of pain in her hands. An x-ray is ordered:



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Based on the x-ray findings, what is the most likely diagnosis?

[Gout11%](#)[Primary hyperparathyroidism16%](#)[Rheumatoid arthritis19%](#)[Osteoarthritis47%](#)[Paget's disease7%](#)

The distribution of joint problems (mainly distal interphalangeal joints and carpometacarpal joints) and changes seen (loss of joint space, subchondral sclerosis) points to a diagnosis of osteoarthritis.

### **Osteoarthritis: x-ray changes**

X-ray changes of osteoarthritis

- decrease of joint space
- subchondral sclerosis
- subchondral cysts
- osteophytes forming at joint margins

Question 3 of 13

A 74-year-old woman complains of neck pain and stiffness. This has gradually developed over the past few years and is now at a point where she only has limited movement. A cervical spine film is requested:



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Based on the cervical spine film, what is the most likely diagnosis?

[Rheumatoid arthritis](#)13%[Osteoarthritis](#)22%[Ankylosing spondylitis](#)53%[Multiple myeloma](#)4%[Paget's disease](#)8%

The x-ray shows complete fusion of the anterior and posterior element resulting in a 'bamboo spine'.

### **Ankylosing spondylitis: investigation and management**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

## **Investigation**

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis



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40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



© Image used on license from [Radiopaedia](#)



Ankylosing spondylitis with well formed syndesmophytes



© Image used on license from [Radiopaedia](#)



Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine





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Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



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Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

## Management

The following is partly based on the 2010 EULAR guidelines (please see the link for more details):

- encourage regular exercise such as swimming
- physiotherapy
- NSAIDs are the first-line treatment
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement

- the 2010 EULAR guidelines suggest: '*Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments*'
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease

#### Question 4 of 13

A 52-year-old female has presented to your neurology clinic reporting difficulty in lifting her arms during exercises at the gym over the past two months. She is distressed by her symptoms and is tearful, mentioning that she is also using significant amounts of make-up to cover a new purple rash and swelling around her eyelids. She reports no past medical history no recent trauma and is normally fit and well. She has had a dry cough for the past 5 months that she puts down to her previous social smoking when she would smoke up to 2 cigarettes whilst going out with friends every 2 weeks.

On examination, you note a limited range of passive movement in both shoulders and hips secondary to tender deltoids and hip flexors. Examination of power demonstrates 4- out of 5 symmetrically in hip flexion and shoulder abduction. An elliptical erythematous rash is present around her eyes, the skin around her fingers appear tough bilaterally. Auscultation of her chest reveals bibasal fine inspiratory crackles and normal heart sounds. Observations show she is currently has a low-grade temperature of 37.7 degrees. A chest radiograph demonstrates bilateral fibrotic changes.

Her admission blood tests are as follows:

Hb	121 g/l
Platelets	$590 \times 10^9/l$
WBC	$12.3 \times 10^9/l$
ESR	20 mm/hr
Creatine kinase	3000 u/l
LDH	250 u/l

What is the most likely unifying diagnosis?

[Inclusion body myositis4%](#)[Systemic sclerosis6%](#)[Dermatomyositis83%](#)[Polymyalgia rheumatica4%](#)[Fibromyalgia3%](#)

The patient has presented with a syndrome of proximal myopathy associated with a violaceous rash on her eyelid and mechanics hands, in addition to possible interstitial lung disease. The most suspicious diagnosis is an inflammatory myositis. Inclusion body myositis is a diagnosis of exclusion and is normally isolated to proximal and less commonly distal, bulbar and facial

muscles. Systemic sclerosis is a possible diagnosis and can produce inflammatory myositis similar to polymyositis. However, cranial and peripheral neuropathies are more common. The distinctive cutaneous features in this patient are strongly suggestive of dermatomyositis: the violaceous eyelid rash and oedema is a heliotropic rash associated with dermatomyositis. Other cutaneous findings include Gottron's papules (violaceous papules on the extensor surfaces of fingers), shawl and V sign (photosensitive hyperpigmentation around the shoulders and upper chest), mechanics hands and periungual erythema. Note the normal ESR result, which is often not elevated in dermatomyositis patients.

## **Dermatomyositis**

### Overview

- an inflammatory disorder causing symmetrical, proximal muscle weakness and characteristic skin lesions
- may be idiopathic or associated with connective tissue disorders or underlying malignancy (typically ovarian, breast and lung cancer, found in 20-25% - more if patient older)
- polymyositis is a variant of the disease where skin manifestations are not prominent

### Skin features

- photosensitive
- macular rash over back and shoulder
- heliotrope rash in the periorbital region
- Gottron's papules - roughened red papules over extensor surfaces of fingers
- nail fold capillary dilatation

### Other features

- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

### Investigations

- the majority of patients are ANA positive, with around 25% anti-Mi-2 positive

#### Question 5 of 13

You see a 48-year-old woman who presents with increasing pain whilst writing notes in her new job as a secretary. She describes a pain in her upper forearm which develops whilst she is writing. This is only relieved when she stops writing and it progresses through the working day. On examination, she has elbow pain with wrist dorsiflexion and middle finger extension. There is no weakness. What is the most likely diagnosis?

[Osteoarthritis4%](#) [Olecranon bursitis16%](#) [Carpal tunnel syndrome13%](#) [Tennis elbow48%](#) [Golfer's elbow19%](#)

Tennis elbow or lateral epicondylitis is essentially a repetitive strain injury of the extensor muscles of the forearm which inserts at the lateral epicondyle of the elbow. Typically this causes pain at the lateral epicondyle area which is exacerbated by gripping small objects and twisting motions such as opening a jar. On examination, passive extension of the wrist with the elbow in full extension reproduces the pain. Pain can also be brought on by middle finger extension.

Like other sprains and strains, it is treated conservatively with analgesia, rest, cold compresses and sometimes physiotherapy.

### **Lateral epicondylitis**

Lateral epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow'). It is most common in people aged 45-55 years and typically affects the dominant arm.

#### Features

- pain and tenderness localised to the lateral epicondyle
- pain worse on wrist extension against resistance with the elbow extended or supination of the forearm with the elbow extended
- episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks

#### Management options

- advice on avoiding muscle overload
- simple analgesia
- steroid injection
- physiotherapy

#### Question 6 of 13

A 75-year-old male presents to the emergency department with two episodes of loss of consciousness over the last 48 hours. Both episodes were witnessed by his wife, onset while sitting in his chair at home, without any witnessed limb jerking, urinary incontinence or tongue biting. He denies any chest pain or shortness of breath normally but reports gradually being able to walk increasingly shorter distances, which he attributed to old age. He has no other significant past medical history, lives with his wife and is a lifelong non-smoker. On examination, he has a significant thoracic kyphosis. On flexion of the lower back, the marked distance increased from 15 cm to 18 cm. He also has a poverty of spinal lateral flexion and bilateral spinal rotation. His cardiovascular examination reveals heart sounds I and II with an early diastolic murmur. Respiratory examination reveals fine inspiratory crackles at both apices. His lying and standing blood pressures are unremarkable. A CT head demonstrated only mild microangiopathic disease. The patient is currently comfortable and alert, requesting to go home. He is attached to cardiac telemetry. What do you expect his ECG to show?

[Sinus bradycardia9% Trigeminy11% Fast atrial fibrillation with ventricular response greater than 1009% Atrial flutter5% Bradycardia with 1st degree heart block67%](#)

The clinical description is of a patient with ankylosing spondylitis, associated with multiple extra-articular features, commonly remembered by MRCP candidates as the As. They classically include atlantoaxial subluxation, arachnoiditis, apical fibrosis, anterior uveitis, aortitis, aortic regurgitation, AV block, amyloidosis, IgA nephropathy, Achilles tendonitis and associations with plantar fasciitis and inflammatory bowel disease (the last two are a bit of a stretch!). In this case, the patient is Schober's positive with a murmur of aortic regurgitation from aortitis. The most likely cause of these episodes of syncope are cardiac in origin. AV node block results in first-degree heart block on ECG, resulting in symptoms if bradycardia leads to transient cerebral hypoperfusion.

#### **Ankylosing spondylitis: features**

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in

males (sex ratio 3:1) aged 20-30 years old.

### Features

- typically a young man who presents with lower back pain and stiffness of insidious onset
- stiffness is usually worse in the morning and improves with exercise
- the patient may experience pain at night which improves on getting up

### Clinical examination

- reduced lateral flexion
- reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- reduced chest expansion

### Other features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis
- and cauda equina syndrome
- peripheral arthritis (25%, more common if female)

### Question 7 of 13

A 54-year-old man presents to Gastroenterology outpatient clinic, for review of his Crohn's disease which was diagnosed 3 years ago. His other past medical history includes ischaemic heart disease, hypercholesterolaemia and gout. He has been suffering from a few months of increased diarrhoea and abdominal pain, and you feel he would benefit from starting azathioprine. Which medication is it important to ensure he is not taking before commencing azathioprine?

[Ramipril5%Allopurinol76%Losartan5%Aspirin5%Simvastatin8%](#)

Allopurinol inhibits the enzyme xanthine oxidase (XO). This enzyme is also required to inactivate 6-mercaptopurine (the active agent from azathioprine). When XO is inhibited, this causes an

increase in 6-mercaptopurine levels, which are then shunted down a different metabolic pathway, leading to higher levels of 6-thioguanine metabolites. These are incorporated into the DNA of white blood cells, leading to reduced activation and reduced replication potential.

Coadministration of azathioprine and allopurinol requires dose reductions and extra monitoring for life threatening agranulocytosis. The other medications listed do not interact with azathioprine and require no extra monitoring.

## **Azathioprine**

Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis. A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.

Adverse effects include

- bone marrow depression
- nausea/vomiting
- pancreatitis

A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.

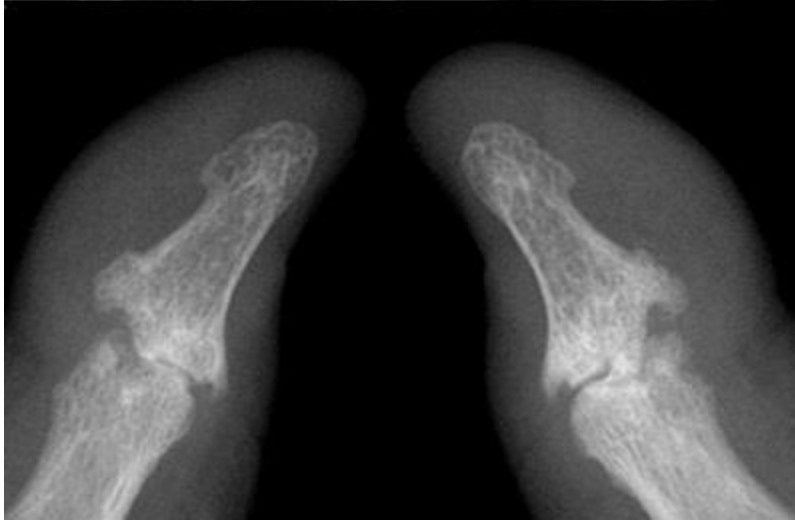
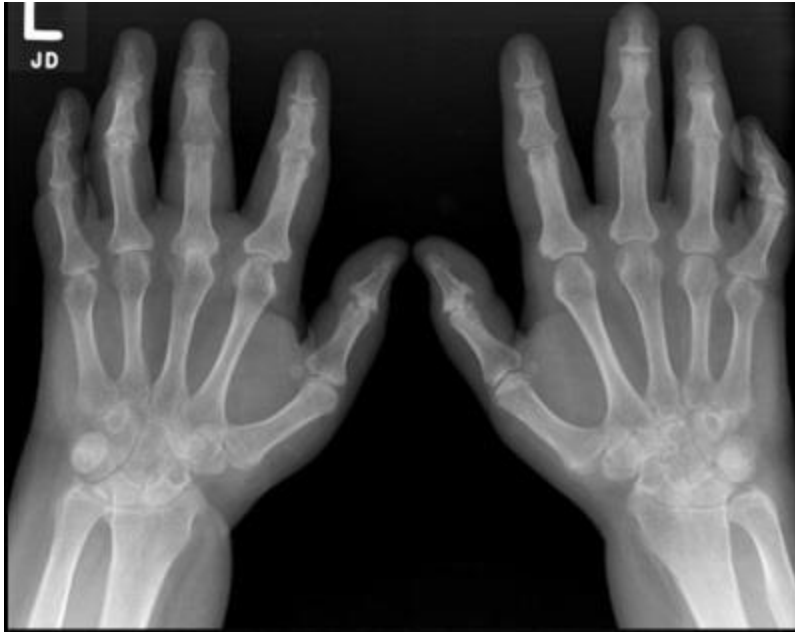
### **Question 8 of 13**

A 54-year-old man is referred to rheumatology with a 6 month history of pain and stiffness in his fingers. He had also been feeling generally tired for the past few weeks. His GP has performed blood tests which show the following:

Hb	13.1 g/l
Platelets	$411 \times 10^9/l$
WBC	$4.5 \times 10^9/l$
CRP	35 mg/l
Rheumatoid factor	Negative

An x-ray of his hands is shown below:







What is the most likely diagnosis?

[Gout 10% Psoriatic arthritis 57% Osteoarthritis 11% Rheumatoid arthritis 11% Hyperparathyroidism 11%](#)

The x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progression towards a 'pencil-in-cup' changes.

## **Psoriatic arthropathy**

Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions. Around 10-20% percent of patients with skin lesions develop an arthropathy with males and females being equally affected

Types\*

- rheumatoid-like polyarthritis: (30-40%, most common type)
- asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- sacroilitis
- DIP joint disease (10%)
- arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

Management

- treat as rheumatoid arthritis
- but better prognosis



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Notice the nail changes on this image as well



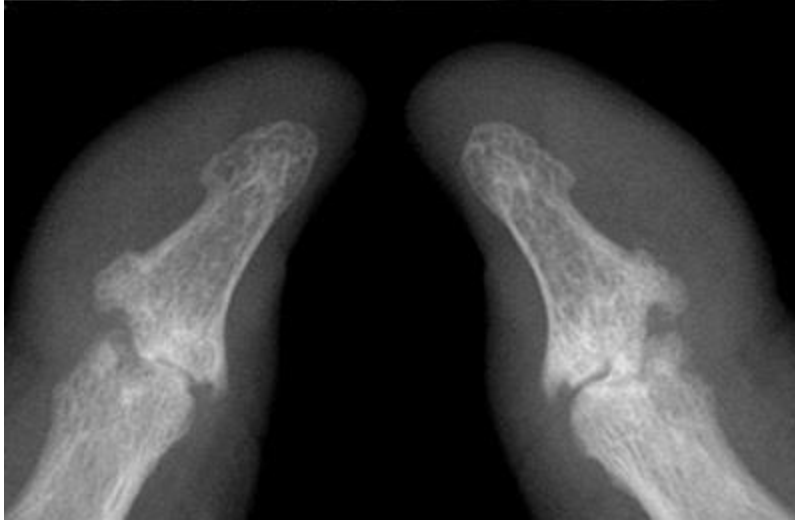
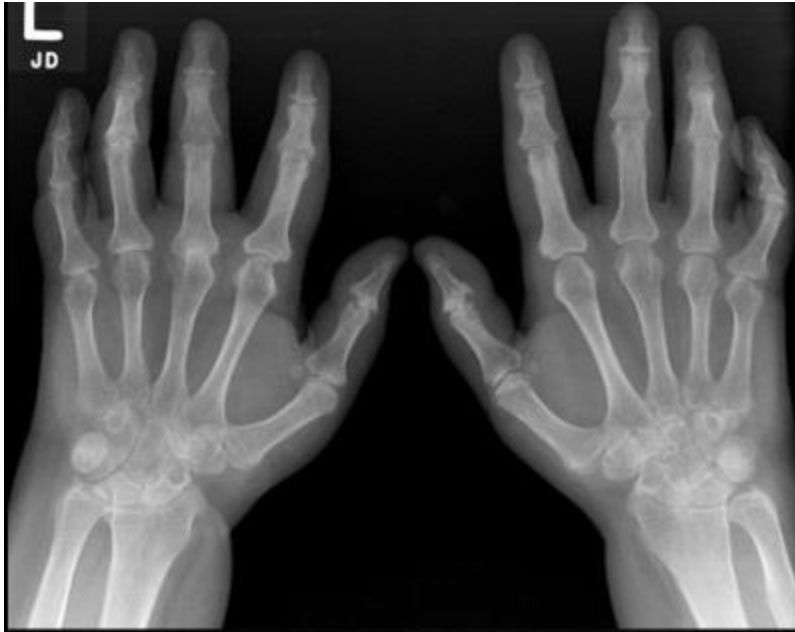
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X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.





This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progression towards a 'pencil-in-cup' changes.

\*Until recently it was thought asymmetrical oligoarthritis was the most common type, based on data from the original 1973 Moll and Wright paper. Please see the link for a comparison of more recent studies

### Question 9 of 13

A 54-year-old lady with a back pain is being managed with 1g paracetamol four times a day and ibuprofen which has been titrated up to the maximum dose of 2.4g/daily. Although she is tolerating this well, she is still complaining of ongoing pain. What is the best option to improve her pain control?

[Stop paracetamol, continue ibuprofen and commence naproxen5%](#) [Continue paracetamol, continue ibuprofen and commence naproxen7%](#) [Stop paracetamol, stop ibuprofen and commence morphine9%](#) [Continue paracetamol, stop ibuprofen and commence naproxen53%](#) [Continue paracetamol, continue ibuprofen and commence morphine25%](#)

Mild to moderate pain should be managed in a stepwise fashion:

Step 1 - paracetamol. Increase to the maximum dose of 1 gram four times a day, before switching to (or combining with) another analgesic.

Step 2 - substitute the paracetamol with ibuprofen and increase the dose of ibuprofen to a maximum of 2.4 grams daily

Step 3 - add paracetamol to ibuprofen

Step 4 - continue with paracetamol 1 gram four times a day. Replace the ibuprofen with an alternative NSAID (such as naproxen)

Step 5 - start a full therapeutic dose of a weak opioid in addition to full-dose paracetamol (1 gram four times a day) and/or an NSAID.

Two NSAIDs should not be used concomitantly as this increases the risk of adverse effects and it is too early to start using a strong opioid such as morphine for this patient. Therefore the best answer is to continue paracetamol and switch the ibuprofen to naproxen.

Please see the NICE CKS for more information:

<http://cks.nice.org.uk/analgesia-mild-to-moderate-pain#!scenario>

## Lower back pain

Lower back pain (LBP) is one of the most common presentations seen in practice. Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

	<b>May be acute or chronic</b>
<b>Facet joint</b>	<b>Pain worse in the morning and on standing</b> <b>On examination there may be pain over the facets. The pain is typically worse on extension of the back</b>
<b>Spinal stenosis</b>	Usually gradual onset Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis
<b>Ankylosing spondylitis</b>	Typically a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if female)
<b>Peripheral arterial disease</b>	Pain on walking, relieved by rest Absent or weak foot pulses and other signs of limb ischaemia Past history may include smoking and other vascular diseases

Question 10 of 13

A 54-year-old woman with a background of rheumatoid arthritis is being managed with a weekly dose of 15mg of methotrexate. She has presented for regular review and her blood tests indicate that she has had a significant fall in her cell counts. It is thought that she has methotrexate induced bone marrow failure.

Hb 110 g/l  
Platelets  $135 \times 10^9/l$   
WBC  $3 \times 10^9/l$   
Neutrophils  $1.9 \times 10^9/l$

What is the best management option?

[Folinic acid44% Ferrous sulphate5% Folic acid38% Iron dextran4% Palifermin8%](#)

The recommended treatment for myelosuppression secondary to her methotrexate therapy is with folinic acid rescue therapy.

Palifermin is used for oral mucositis associated with methotrexate treatment for haematological malignancies. Folic acid is used to prevent methotrexate associated side effects. Ferrous sulphate and iron dextran are not indicated in this case as they are used for iron deficiency anaemia.

## **Methotrexate**

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

### **Indications**

- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

### **Adverse effects**

- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis

### **Pregnancy**



- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

#### Prescribing methotrexate

- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

#### Question 11 of 13

A 62-year-old complains of a 6 month history of recurrent pains in both feet. His feet now seem constantly painful although he does go through periods where the pain gets even worse.

An x-ray is requested:



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[Gout 52%](#)[Metastatic prostate cancer 5%](#)[Osteoarthritis 17%](#)[Rheumatoid arthritis 16%](#)[Primary hyperparathyroidism 11%](#)

The x-ray shows multiple periarticular erosions bilaterally with adjacent soft tissue masses and relatively preserved joint spaces. The erosions observed throughout the metatarsal bases bilaterally, as well as throughout the midfoot and hindfoot on the left are likely due, in part, to intraosseous tophi. These changes are consistent with gout.

Even if you are not familiar with the x-ray changes associated with gout the presence of changes around the first metatarsophalangeal should immediately make you think of gout.

## **Gout: features**

Gout is a form of inflammatory arthritis. Patients typically have episodes lasting several days when their gout flares and are often symptom free between episodes. The acute episodes typically develop maximal intensity within 12 hours/ The main features it presents with are:

- pain: this is often very significant
- swelling
- erythema

Around 70% of first presentations affect the 1st metatarsophalangeal (MTP) joint. Attacks of gout affecting this area were historically called podagra. Other commonly affected joints include:

- ankle
- wrist
- knee

If untreated repeated acute episodes of gout can damage the joints resulting in a more chronic joint problem.

Radiological features of gout include:

- joint effusion is an early sign
- well-defined 'punched-out' erosions with sclerotic margins in a juxta-articular distribution, often with overhanging edges
- relative preservation of joint space until late disease
- eccentric erosions
- no periarticular osteopaenia (in contrast to rheumatoid arthritis)
- soft tissue tophi may be seen



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X ray of a patient with gout affecting his feet. It demonstrates juxta-articular erosive changes around the 1st MTP joint with overhanging edges and associated with a moderate soft tissue swelling. The joint space is maintained.



© Image used on license from [Radiopaedia](#)



X-ray of a patient with gout affecting his hands. There are multiple periarticular erosions bilaterally with adjacent large soft tissue masses and relatively preserved joint spaces. In the right hand, these findings are most prominent at the 1st interphalangeal, 2nd-4th proximal interphalangeal, 1st-3rd metacarpophalangeal and carpometacarpal joints. In the left hand, the findings are most prominent at the ulnar styloid, scapholunate joint, first and fifth carpometacarpal joints, second and fifth metacarpophalangeal joints and 1st interphalangeal joint.

#### Question 12 of 13

A 67-year-old woman presents with a rash. For the past two weeks she has felt tired and 'achey'. She also has a dry cough and some pleuritic chest pain. She is most concerned however with a new rash on her face:



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Which drug is most likely to cause this presentation?

[Procainamide](#)58%[Digoxin](#)6%[Sodium valproate](#)13%[Methyldopa](#)12%[Allopurinol](#)11%

## Drug-induced lupus

In drug-induced lupus not all the typical features of systemic lupus erythematosus are seen, with renal and nervous system involvement being unusual. It usually resolves on stopping the drug.

### Features

- arthralgia
- myalgia
- skin (e.g. malar rash) and pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, dsDNA negative
- anti-histone antibodies are found in 80-90%
- anti-Ro, anti-Smith positive in around 5%



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A woman with drug-induced lupus

### Most common causes

- procainamide
- hydralazine

### Less common causes

- isoniazid
- minocycline

- phenytoin

#### Question 13 of 13

A 58-year-old gentleman of Afro-Caribbean origin presents to clinic. He complains of lethargy, fever and joint pain, particularly in both knees. He has also noticed an intermittent rash on his arms and his neck. These symptoms have progressed over the last six months. He has a past medical history of congestive cardiac failure and chronic renal failure secondary to hypertension. His medication includes bisoprolol, aspirin and hydralazine/isosorbide dinitrate.

On examination the patient has no evidence of joint swelling. He has discrete patches of scaling on his neck and forearms. He has normal power in his arms and legs.

The following blood tests were obtained;

Rheumatoid Factor	Positive
Anti-nuclear antibody	Positive
Anti-single stranded DNA	Positive
Anti-extractable nuclear Antigen	Negative
Anti-histone antibodies	Positive

What is the most likely diagnosis?

[Polymorphous Light Eruption5%](#)[Dermatomyositis9%](#)[Drug induced lupus erythematosus68%](#)[Rheumatoid arthritis4%](#)[Systemic lupus erythematosus14%](#)

A polymorphous rash would expect to be erythematous and less associated with systemic symptoms. Dermatomyositis may have a positive ENA (anti-Jo1) with heliotrope rash and Gottrons papules. There also may be associated muscle weakness. Rheumatoid arthritis would expect to show arthritis and is less associated with a rash and the antibody picture. SLE is more associated with double stranded DNA and ENA.

Drug induced lupus can be caused by a variety of drugs but most commonly antihypertensives and antifungals. Specific examples include isoniazid, hydralazine, procainamide, diltiazem and phenytoin. Anti-histone antibodies are associated with drug-induced lupus in most cases.

#### **Drug-induced lupus**

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A woman with drug-induced lupus

#### Most common causes

- procainamide
- hydralazine

#### Less common causes

- isoniazid
- minocycline
- phenytoin





Question 1 of 102

A 57-year-old man attends neurology clinic. He has recently been diagnosed with Parkinson's disease and has agreed to start treatment with cabergoline as monotherapy. He has had a full examination, lung function tests, routine blood tests, chest X-ray and an echocardiogram.

Apart from a clinical review, what investigation is most important to arrange regularly to monitor for complications?

[Chest X-ray30%FBC11%U&E11%Echocardiogram35%LFT13%](#)

The correct answer is echocardiogram. Cabergoline is a dopaminergic drug which can be used to treat Parkinson's disease. Dopaminergic drugs are associated with fibrotic reactions including pulmonary, retroperitoneal and pericardial fibrosis, but cabergoline also associated with development of new valvulopathy. The BNF recommends establishing a baseline set of investigations and then to monitor clinically for dyspnoea, persistent cough, chest pain, cardiac failure and abdominal pain or tenderness.

Source:

Committee, Joint Formulary. British National Formulary (BNF) No. 72. London: Pharmaceutical, 2016.

## **Dopamine receptor agonists**

### **Indications**

- Parkinson's disease
- prolactinoma/galactorrhoea
- cyclical breast disease
- acromegaly

Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, L-dopa is sometimes used as an initial treatment

## Overview

- e.g. bromocriptine, ropinirole, cabergoline, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide\*) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

## Adverse effects

- nausea/vomiting
- postural hypotension
- hallucinations
- daytime somnolence

\*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

## Question 2 of 102

A 17 year old girl is brought to the Emergency Department following a prolonged seizure lasting seven minutes. She is known to suffer from epilepsy and has been stable on lamotrigine for eight years, having on average only one generalised tonic clonic seizure every eight months. Her mother describes an increase in her seizure frequency over the last four weeks; she has had three generalised tonic-clonic seizures during this period, each lasting around three minutes. There have been no changes to stress levels, sleep pattern or diet. She confirms she has however started a new medication for dysmenorrhoea. Which is the most likely to explain this increase in frequency?

[Medroxyprogesterone \(Depo-Provera\)36%](#)  
[Mefenamic acid43%](#)  
[Ibuprofen7%](#)  
[Aspirin6%](#)  
[Naproxen7%](#)

Taking a full medication history is an essential aspect of any history; it can be particularly important in epilepsy, not only to gauge medication compliance and anti-epileptic therapy, but to determine any precipitating factors.

Analgesics that are known to induce seizures or worsen seizure control include fentanyl, mefenamic acid, and tramadol (among others). Other drugs that are known to induce seizures include amitriptyline, aminophylline, isotretinoin and haloperidol.

It is important to be aware of the interaction between contraception and antiepileptic medication;

contraceptive failure, teratogenicity and reduced seizure control are potential effects.

P450 enzyme inducers will decrease the drug level and therefore increase the failure rate of oestrogen and progesterone containing contraceptives.

- Carbamazepine
- Oxcarbazepine
- Phenytoin
- Phenobarbitone
- Primidone
- Topiramate

Lamotrigine is not a P450 inducer. Studies have shown a slight decrease in levonorgestrel levels, although the clinical significance is undetermined. Levels of lamotrigine are reduced by oral contraceptives containing ethinylestradiol, increased seizure frequency may therefore occur. There is no evidence that progestogen-only methods affect lamotrigine levels.

Sources:

- BNF:4.8.1 control of the epilepsies
- Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR). U.S. Medical Eligibility Criteria for Contraceptive Use, (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr59e0528a1.htm>)
- Faculty of sexual and reproductive healthcare clinical effectiveness unit; antiepileptic drugs and contraception. FSRH 2010

### **Prescribing in patients with epilepsy**

The following drugs may worsen seizure control in patients with epilepsy:

- alcohol, cocaine, amphetamines
- ciprofloxacin, levofloxacin
- aminophylline, theophylline
- bupropion
- methylphenidate (used in ADHD)
- mefenamic acid

Some medications such as benzodiazepines, baclofen and hydroxyzine may provoke seizures whilst they are being withdrawn.

Other medications may worsen seizure control by interfering with the metabolism of anti-epileptic drugs (i.e. P450 inducers/inhibitors).

#### Question 4 of 102

A 63-year-old man is commenced on anti-tuberculosis therapy, after presenting hospital with a history of several months of weight loss, shortness of breath and a productive cough which was sometimes accompanied by haemoptysis. A chest x-ray had revealed apical consolidation and sputum was positive for acid-fast bacilli, thus a diagnosis of tuberculosis was then made. His only past medical history includes a diagnosis of asthma for which he takes PRN salbutamol and seretide (25 micrograms of salmeterol and 125 micrograms of fluticasone propionate) inhaler twice daily.

A week after being diagnosed, he is admitted to the acute medical unit with shortness of breath and bilateral expiratory wheeze. His observations reveal a temperature of 37.1°C, respiratory rate of 27 breaths per minute and oxygen saturations of 94% on room air. Oxygen is commenced via a face mask. A chest x-ray reveals the same hilar consolidation as before, with no new features.

What is the most appropriate next step in her treatment?

[Continue the tuberculosis medication at current dose and increase the steroid dose69%](#)[Continue the tuberculosis medication at current dose and decrease the steroid dose9%](#)[Reduce the tuberculosis medication and increase the steroid dose7%](#)[Stop the tuberculosis medication and increase the steroid dose7%](#)[Continue the tuberculosis medication at current dose and keep the steroid dose the same9%](#)

Rifampicin increases the metabolism of corticosteroids, thus patients who are on long-term steroids (as in this case) should receive a higher dose of corticosteroids when starting tuberculosis therapy.

#### **Tuberculosis: drug side-effects and mechanism of action**

Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis, orange secretions
- flu-like symptoms

### Isoniazid

- mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy: prevent with pyridoxine (Vitamin B6)
- hepatitis, agranulocytosis
- liver enzyme inhibitor

### Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- hyperuricaemia causing gout
- arthralgia, myalgia
- hepatitis

### Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- optic neuritis: check visual acuity before and during treatment
- dose needs adjusting in patients with renal impairment

### Question 1 of 101

A 67-year-old woman presents to her GP with symptoms of dysuria and increased urinary frequency. She is otherwise systemically well with no signs of sepsis. Urine dip in the GP surgery shows blood, leukocytes, protein and nitrites. The patients medical history is significant only for asthma for which she takes salbutamol and beclomethasone inhalers, hypertension for which she takes amlodipine 10mg daily and ramipril 5mg daily, and chronic kidney disease, stage 3.

Which of the following antibiotics is best avoided in the treatment of this patients urine infection?

[Amoxicillin6% Augmentin \(amoxicillin and clavulanic acid\)6% Ciprofloxacin12% Nitrofurantoin46% Trimethoprim30%](#)

Nitrofurantoin is best avoided in patients with CKD stage 3 or higher due to the significant risk of treatment failure and occurrence of side effects due to drug accumulation

This question is about antibiotic prescribing in chronic kidney disease (CKD). Many drugs need dose adjustment in renal disease due to changes in drug metabolism and also pharmacokinetics. Often this dose adjustment is made on the level of the estimated glomerular filtration rate (eGFR) which is a calculated surrogate of renal function using the serum creatinine. Stages of chronic kidney disease are classified according to the eGFR; stage 3 CKD equates to an eGFR of 30-59ml/min.

Nitrofurantoin is a relatively old and unique antibiotic which has enjoyed a new lease of life with increasing antibiotic resistance. It is actually an inactive pro-drug which is reduced in vivo to active forms by the bacterial flavoprotein nitrofurantoin reductase, and it is these reduced forms of the drug which exert their antibiotic properties by damaging bacterial proteins. In order to be effective at treating urinary tract infections, nitrofurantoin needs to be concentrated in the urine and an adequate glomerular filtration is required for this to occur. An eGFR of less than 40-60ml/min means that the drug is wholly ineffective as a bactericidal agent and is not recommended in patients with CKD stage 3 or worse due to the likelihood of treatment failure. Coupled with this is the risk of drug toxicity in the patient. Without adequate renal filtration, the drug is likely to accumulate. Although bacterial flavoproteins activate nitrofurantoin more readily, human enzymes can reduce this drug to generate many highly active radical species, which can cause side effects including peripheral neuropathy, which may not be reversible, hepatotoxicity and acute and chronic pulmonary reactions and fibrosis.

Patients taking nitrofurantoin should be advised that this drug will discolour the urine. It is also a safe drug to use in pregnancy except at full term when there is a risk of haemolysis in the neonate.

Amoxicillin and co-amoxiclav are widely used antibiotics in the treatment of urinary tract infections and are relatively safe in renal impairment. Dose reduction is recommended in severe chronic renal disease, i.e. an eGFR <15-30ml/min to avoid the risk of crystalluria. Similarly, a reduction in dose is necessary for ciprofloxacin in CKD to avoid crystalluria although this is recommended from an eGFR of 30-60ml/min.

Trimethoprim is an antibiotic which is entirely safe to use in all but the most severe forms of chronic kidney disease where a modest dose adjustment is required. It should be noted however that use of trimethoprim is likely to affect the results of renal function tests since the drug inhibits tubular secretion of creatinine leading to a rise in serum levels in all patients, including those with previously normal renal function. This is without any effect on the glomerular filtration rate.

## Prescribing in patients with renal failure

Questions regarding which drugs to avoid in renal failure are common

Drugs to avoid in renal failure

- antibiotics: tetracycline, nitrofurantoin
- NSAIDs
- lithium
- metformin

Drugs likely to accumulate in chronic kidney disease - need dose adjustment

- most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- digoxin, atenolol
- methotrexate
- sulphonylureas
- furosemide
- opioids

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin

### Question 1 of 97

A 19 year old man was brought by his friends to the Emergency Department after becoming unwell on a night out. He had collapsed while dancing then felt very anxious and jittery. On close questioning the patient confessed to taking three tablets of ecstasy during his night out. He had also drunk two beers but insisted he had kept himself hydrated with water later on in the evening. The patient had no past medical history and took no regular medications.

Initial assessment was as documented below.

Airway



- Patient's own

### Breathing

- Respiratory rate 20 / minute
- No respiratory distress
- O2 saturations 99 % (air)
- Clear lung fields with air entry throughout

### Circulation

- Mild-moderate dehydration
- HR 110 bpm regular
- BP 176 / 95 mmHg
- JVP not elevated
- Heart sounds normal

### Disability

- Temperature 37.5°C
- GCS 15/15; anxious
- Pupils equal and reactive to light
- Full range of eye movements
- Good power of arms and legs
- Slight increased tone in arms and legs, 6 beats of clonus inducible on angle dorsiflexion
- Generalised hyper-reflexia

### Exposure

- Abdomen soft and non-tender
- No evidence of external or bony injury

Results of a venous blood sample are given below.

pH            7.36  
 Bicarbonate 24.6 mmol / L (20.0-26.0)  
 Base excess -0.9 mmol / L  
 Sodium      136 mmol / L  
 Potassium   4.5 mmol / L  
 Lactate      1.8 mmol / L

What is the correct management of this patient?

[Intravenous chlorpromazine 5% Oral cyproheptadine 13% Oral diazepam 18% Intravenous midazolam 8% Slow intravenous fluids; observation 55%](#)

The patient is presenting with symptoms and signs of mild serotonin syndrome and dehydration secondary to ecstasy use. There are no signs of moderate or severe serotonin syndrome such as opiclonus, sustained clonus, rigidity, reduced consciousness or agitation or severe hyperthermia. Supportive care is the most appropriate treatment in this case.

Oral or intravenous benzodiazepines can reduce agitation and muscle hyper-activity in moderate to severe presentations. Intravenous or oral serotonin antagonists such as chlorpromazine or cyproheptadine may also be used if necessary.

Buckley N, Dawson A, Isbister G. Serotonin syndrome. BMJ 2014;348:g1626.

## **Serotonin syndrome**

### Causes

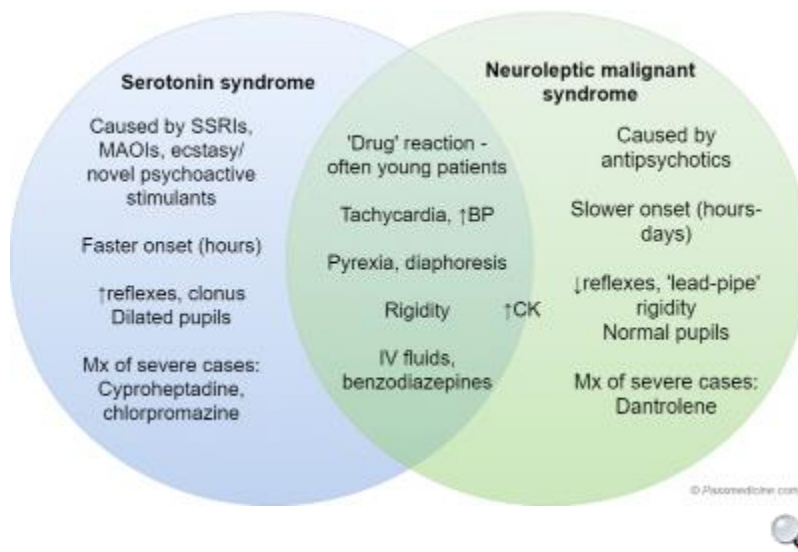
- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines

### Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state

### Management

- supportive including IV fluids
- benzodiazepines
- more severe cases are managed using serotonin antagonists such as cyproheptadine and chlorpromazine



Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

#### Question 2 of 97

A 77-year-old woman with a long history of atrial fibrillation comes to the Emergency department following a collapse at the local supermarket. She is treated with digoxin for rate control, and anti-coagulated with warfarin. Apparently she has been unwell with diarrhoea over the past few days but has continued to take her regular medication. On examination her blood pressure is 90/50 mmHg, pulse is 88 beats per minute and regular. You note short runs of ventricular tachycardia on the monitor whilst you are listening to her chest. Bloods include:

Na<sup>+</sup> 145 mmol/l  
 K<sup>+</sup> 3.5 mmol/l  
 Urea 14.1 mmol/l  
 Creatinine 188 µmol/l  
 Digoxin 3 nmol/l

Which of the following is the most appropriate intervention?

[Amiodarone22%](#) [Flecainide8%](#) [Verapamil8%](#) [Magnesium36%](#) [Phenytoin26%](#)

This patient has digoxin toxicity, with toxicity considered a possibility once digoxin levels breach a level of 2 nmol/l. It's likely the collapse has been precipitated both by dehydration related to the acute GI illness and potentially a short run of arrhythmia.

Phenytoin is the correct answer, it has class 1B anti-arrhythmic activity, and is recognised as a therapeutic option for patients with digoxin toxicity. Lignocaine has similar class 1B activity, but is often less well tolerated in IV infusion. Phenytoin is usually administered as a loading dose of 15mg/kg.

Amiodarone is not an effective anti-arrhythmic in this situation, and is recognised in chronic use to lead to an increase in digoxin levels. Flecainide is also known to increase digoxin levels when the two are used together over a prolonged period, and it is not used acutely in the management of digoxin related VT. Calcium channel blockers such as verapamil are effective in controlling heart rate in SVT, and magnesium is used in the treatment of torsades de pointes VT related to QT prolongation.

<https://www.mja.com.au/journal/2013/199/3/phenytoin-old-effective-antiarrhythmic-agent-suppression-ventricular-tachycardia>

## **Digoxin and digoxin toxicity**

Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation. As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.

Mechanism of action

- decreases conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter
- increases the force of cardiac muscle contraction due to inhibition of the  $\text{Na}^+/\text{K}^+$  ATPase pump. Also stimulates vagus nerve

## **Digoxin toxicity**

Plasma concentration alone does not determine whether a patient has developed digoxin toxicity. The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.

Features

- generally unwell, lethargy, nausea & vomiting, anorexia, confusion, yellow-green vision
- arrhythmias (e.g. AV block, bradycardia)
- gynaecomastia

## Precipitating factors

- classically: hypokalaemia\*
- increasing age
- renal failure
- myocardial ischaemia
- hypomagnesaemia, hypercalcaemia, hypernatraemia, acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- drugs: amiodarone, quinidine, verapamil, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), ciclosporin. Also drugs which cause hypokalaemia e.g. thiazides and loop diuretics

## Management

- Digibind
- correct arrhythmias
- monitor potassium

\*hyperkalaemia may also worsen digoxin toxicity, although this is very small print

## Question 3 of 97

A 44-year-old man presents to the emergency department complaining of breathlessness. He reports that he was leaving a restaurant because he was starting to feel lightheaded, developed a headache and was breathless.

An ABG done on admission demonstrated carbon monoxide at 26%.

Three hours later he feels tired and weak, but his headache and lightheadedness have improved since admission. He has a past medical history of asthma which he reports to be well controlled, rarely needing his blue inhaler. He smokes 15-cigarettes per day and has a 23 pack-year history. He works as a teacher in central London. On examination, he is receiving 15L of oxygen via a non-rebreather mask. His chest is clear on auscultation. Neurological examination is normal. An ECG demonstrates no ischaemic changes.

## Observations:

Saturations      100%

Respiratory rate 16/min  
Blood pressure 126/87mmHg  
Heart rate 84/min  
Temperature 36.8°C

What is the most appropriate management plan?

[Wean off oxygen guided by standard pulse oximetry saturation levels9%Prescribe IV mannitol4%Maintain high-flow oxygen until asymptomatic or carbon monoxide levels are <10%65%Refer urgently for hyperbaric oxygen treatment17%Arrange urgently for non-invasive ventilation5%](#)

The answer is to maintain high-flow oxygen until asymptomatic or carbon monoxide levels are <10%. Weaning off oxygen is not appropriate to be guided by pulse oximetry as standard pulse oximetry will detect carbon monoxide bound haemoglobin as well and are therefore falsely reassuring. IV mannitol is indicated if cerebral oedema is anticipated, such as in severe cases, or established. Hyperbaric oxygen again also reserved for severe cases or pregnancy, and non-invasive ventilation has no role in carbon monoxide poisoning.

Source:

'Carbon Monoxide Poisoning.' BMJ Best Practice. N.p., 06 July 2015.

## **Carbon monoxide poisoning**

Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia. There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK

Questions may hint at badly maintained housing e.g. student houses

Features of carbon monoxide toxicity

- headache: 90% of cases
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

### Typical carboxyhaemoglobin levels

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting
- > 30% severe toxicity

### Management

- 100% oxygen
- hyperbaric oxygen

### Indications for hyperbaric oxygen\*

- loss of consciousness at any point
- neurological signs other than headache
- myocardial ischaemia or arrhythmia
- pregnancy

\*as stated in the 2008 Department of Health publication 'Recognising Carbon Monoxide Poisoning'

### Question 4 of 97

A 48-year-old farmer is found in a state of distress having collapsed whilst mixing insecticides in his barn. On arrival in the Emergency department, he is confused, salivating excessively, and has been incontinent of urine and faeces. You note noisy breathing, his blood pressure is 90/60 mmHg, with a pulse of 48 beats per minute.

Which of the following is the most appropriate intervention?

[Atropine75%Hyoscine6%Glucagon7%NG activated charcoal7%Noradrenaline5%](#)

The clue here is insecticide exposure, coupled with evidence of muscarinic effects of organophosphate poisoning including excessive secretions, incontinence, hypotension and bradycardia. Time is of the essence, and administration of atropine in this situation may be life-saving.

Pralidoxime is also used once atropine has been administered, although it's additive benefit is debated.

Hyoscine is less potent versus atropine and is mainly used in palliative care to manage pain from the gastrointestinal tract and excessive respiratory secretions. Glucagon is used as a treatment for beta-blocker overdose. Activated charcoal may be of value but is subsidiary to use of anticholinergics. Anticholinergics are also preferred to sympathetic agonists such as noradrenaline.

## **Organophosphate insecticide poisoning**

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

- Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

### **Management**

- atropine
- the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit

### **Question 5 of 97**

A 17-year-old woman with a history of epilepsy and deliberate self-harm is brought into the emergency department with a Glasgow coma score of 13 (E3 V4 M6) and respiratory rate of 8/min.

On examination, her pulse is 56/min and regular, blood pressure 110/60 mmHg and her chest is clear. She has no signs of injury but an empty packet of diazepam was found in her handbag. Whilst the patient is breathing room air a nurse in the emergency department has taken an arterial blood gas shown below.



pH 7.39  
pO<sub>2</sub> 10.1 kPa  
pCO<sub>2</sub> 5.6 kPa  
BE 0.8 mEq/l

What is the best initial management?

[Flumazenil 200mcg infused IV over 15 minutes](#)24%[Flumazenil 200mcg bolus IV over 15 seconds](#)16%[Naloxone 400mcg IM injection](#)7%[Urgent intubation with anaesthetic support](#)15%[Supportive care only](#)38%

The blood gas shows her ventilation appears inadequate but at this stage the best management is supportive, allowing levels of diazepam to reduce over time, something that can be easily assessed clinically with and with the aid of an arterial blood gas sample.

Administering the benzodiazepine antidote flumazenil to an epileptic puts her at high risk of seizures. Naloxone is an antidote to opiate overdose. If however despite simple manoeuvres her ventilation deteriorated or GCS dropped to less than 8, anaesthetic support should be sought.

## Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Treatment
	Management
Paracetamol	<ul style="list-style-type: none"><li>activated charcoal if ingested &lt; 1 hour ago</li><li>N-acetylcysteine (NAC)</li><li>liver transplantation</li></ul>
	Management
Salicylate	<ul style="list-style-type: none"><li>urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning</li><li>haemodialysis</li></ul>
Opioid/opiates	Naloxone
Benzodiazepines	Flumazenil

Toxin	Treatment
<b>Tricyclic antidepressants</b>	Management <ul data-bbox="516 317 1422 646" style="list-style-type: none"> <li>• IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity</li> <li>• arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias</li> <li>• dialysis is ineffective in removing tricyclics</li> </ul>
	Management <ul data-bbox="516 764 1422 982" style="list-style-type: none"> <li>• mild-moderate toxicity may respond to volume resuscitation with normal saline</li> <li>• haemodialysis may be needed in severe toxicity</li> <li>• sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion</li> </ul>
<b>Warfarin</b>	Vitamin K, prothrombin complex
<b>Heparin</b>	Protamine sulphate
<b>Beta-blockers</b>	Management
	<ul style="list-style-type: none"> <li>• if bradycardic then atropine</li> <li>• in resistant cases glucagon may be used</li> </ul>
<b>Ethylene glycol</b>	Management has changed in recent times
	<ul style="list-style-type: none"> <li>• ethanol has been used for many years</li> <li>• works by competing with ethylene glycol for the enzyme alcohol dehydrogenase</li> <li>• this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning</li> <li>• <b>fomepizole</b>, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol</li> <li>• haemodialysis also has a role in refractory cases</li> </ul>
<b>Methanol poisoning</b>	Management
	<ul style="list-style-type: none"> <li>• fomepizole or ethanol</li> </ul>

Toxin	Treatment
	<ul style="list-style-type: none"> <li>haemodialysis</li> </ul>
	Management
<b>Organophosphate insecticides</b>	<ul style="list-style-type: none"> <li>atropine</li> <li>the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit</li> </ul>
<b>Digoxin</b>	Digoxin-specific antibody fragments
<b>Iron</b>	Desferrioxamine, a chelating agent
<b>Lead</b>	Dimercaprol, calcium edetate
	Management
<b>Carbon monoxide</b>	<ul style="list-style-type: none"> <li>100% oxygen</li> <li>hyperbaric oxygen</li> </ul>
<b>Cyanide</b>	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate

#### Question 1 of 92

A 63 year old farmer is brought to the Emergency Department after falling into a trough of organophosphate sheep dip. On arrival in the department he is in extremis with profuse vomiting and productive of copious respiratory secretions. His airway is threatened but he is also agitated and difficult to assess. Respiratory rate is 20 breaths per minute and oxygen saturations are 87% on 4L/min oxygen. Wheeze is audible from the end of the bed. The heart rate is 55bpm and the blood pressure is 92/44mmHg. Heart sounds are normal. He is incontinent of urine and faeces and has severe abdominal pain. There is widespread muscle fasciculation and global weakness. Pupils are pinpoint.

Which of the following best describes the toxic action of organophosphate compounds?

[Adrenergic blockade due to competitive inhibition of  \$\alpha\_1\$ ,  \$\alpha\_2\$ ,  \$\beta\_1\$  and  \$\beta\_3\$  receptors9%](#)  
[Adrenergic upregulation due to inhibition of monoamine oxidase5%](#)  
[Cholinergic upregulation due to inhibition of acetylcholinesterase51%](#)  
[Cholinergic upregulation due to direct activation at muscarinic M1, M2 and M3 receptors23%](#)  
[Cholinergic upregulation due to direct activation at nicotinic CNS and muscle receptors12%](#)

Organophosphate poisoning occurs due to inhibition of acetylcholinesterase leading to upregulation of nicotinic and muscarinic cholinergic neurotransmission

Organophosphate insecticides are highly effective pesticidal agents. They work by binding to and irreversibly inactivating the enzyme acetylcholinesterase (AChE) which is essential for respiration in insects. Unfortunately, they also inhibit AChE in humans too, which exerts toxic effects when inadvertent exposure occurs occupationally, and this class of agents can also be used as a chemical weapon in the form of nerve gases.

Due to the non-specificity of acetylcholinesterase in cholinergic synapses, inhibition of the enzyme leads to upregulation of neurotransmission at all cholinergic synapses, giving rise to both nicotinic and muscarinic symptoms. Classically, the muscarinic symptoms seen can be remembered by the mnemonic SLUDGE: salivation, lacrimation, urination, defecation, gastrointestinal pain, emesis, and also pupillary constriction, bronchoconstriction and bradycardia. Nicotinic symptoms include headache, anxiety, fasciculations, weakness, ataxia, confusion and respiratory depression. Sometimes there is variation in the extent of symptoms observed due to the relative upregulation of each neurotransmitter symptom with either predominant nicotinic symptoms or muscarinic ones, for example either bradycardia due to muscarinic overdrive or tachycardia due to nicotinic drive.

Knowledge of the pathophysiological effects of organophosphates is important because it guides treatment. Severe exposure to organophosphates may cause death within minutes due to respiratory failure. Provision of supplemental oxygen is important. The first life-saving intervention which may be provided is intravenous atropine which is a competitive antagonist at muscarinic receptors, predominantly subtypes M1, M2 and M3. This increases heart rate and improves respiratory function by relaxing bronchial smooth muscle and drying secretions. Atropine administration may need to be repeated multiple times at doses up to 2mg every five minutes until heart rate is above 80. Definitive treatment may be provided by administration of pralidoxime or obidoxime which are oxime drugs which bind to an allosteric moiety of AChE and causes a conformational change in the enzyme allowing it to be released from the organophosphate. Organophosphates irreversibly bind to AChE when in their physiological state but conformational change by oximes allows this to be undone. This is time dependent however and a process known as aging occurs whereby the longer the enzyme is inhibited the less likely the oxime is to be able to reanimate it. In warfare, soldiers are often supplied with auto-injectors containing atropine, pralidoxime and midazolam as an immediate response to exposure to nerve agents.

While exposure to organophosphates often produces hypotension and bradycardia with bronchoconstriction, they have no effect on adrenergic neurotransmission.

It is also important to note that organophosphate exposure is from environmental sources and as such decontamination is vital to prevent exposure to healthcare providers and appropriate personal protective equipment must be worn by rescuers.

## **Organophosphate insecticide poisoning**

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

- Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

Management

- atropine
- the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit

Question 2 of 92

A 65-year-old gentleman presents with a chronic cough. He has noticed a productive cough for several months with a few episodes of mild haemoptysis. He has also noticed mild weight loss and night sweats. He has traveled to India several times during the year. A sputum sample is positive for acid-fast bacilli. Before starting treatment, what examination should he be assessed for?

[Visual acuity79%Hearing7%Sense of smell5%Sense of taste4%Eye movements5%](#)

The correct answer is visual acuity. This is a patient who is very likely to have tuberculosis and will need treatment with rifampicin, isoniazid, pyrazinamide and ethambutol. As ethambutol can cause optic neuritis it is advised that visual acuity should be assessed before starting treatment. Hearing and sense of smell are unlikely to be affected by the treatment and therefore routine assessment is not needed. The sense of taste should remain normal but the patient should be warned that secretions, including saliva, will change colour and that this is normal. Eye movements are unlikely to be affected as well.

**Tuberculosis: drug side-effects and mechanism of action**

## Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis, orange secretions
- flu-like symptoms

## Isoniazid

- mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy: prevent with pyridoxine (Vitamin B6)
- hepatitis, agranulocytosis
- liver enzyme inhibitor

## Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- hyperuricaemia causing gout
- arthralgia, myalgia
- hepatitis

## Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- optic neuritis: check visual acuity before and during treatment
- dose needs adjusting in patients with renal impairment

## Question 1 of 89

A 28-year-old lady is brought in by her mother having taken an overdose of an unknown medication. She has recently broken up with her boyfriend and has been fired from her job for turning up late to work persistently. She was found in her room by her mother with a small bottle of vodka which was empty and some burnt medication packaging. She has no history of mental health disease, although did self-harm (arm cutting) twice whilst a teenager. She has no medical history other than being treated for malaria during a recent trip to west Africa. The patient is

tearful, regrets the overdose and is currently complaining of nausea, epigastric discomfort, slightly blurred vision and a ringing in her ears.

On examination, her heart rate is 115 beats/min, her blood pressure 98/48 mmHg and she appears flushed. Her respiratory rate is 18 breaths per minute and her oxygen saturations 98% breathing room air. Her Glasgow coma score is 15/15 and her pupils are equal and reactive. Her blood results are as follows.

Na <sup>+</sup>	135 mmol/l
K <sup>+</sup>	4.3 mmol/l
Urea	5.1 mmol/l
Creatinine	86 µmol/l
Bilirubin	18 µmol/l
ALP	65 u/l
ALT	56 u/l

What is the most likely toxin?

[Quinine overdose65%](#)[Ibuprofen overdose10%](#)[Alcohol intoxication6%](#)[Paracetamol overdose6%](#)[Malarone overdose13%](#)

Cinchonism is the syndrome described (blurred vision, tinnitus, nausea...) and can be secondary to quinine or quinidine ingestion as an overdose, but also less commonly with normal dosing. Although uncommon in the western world use of quinine as a drug in overdose is not uncommon in malaria endemic areas such as south-east Asia. The tinnitus may be associated with transient loss of high frequency hearing loss. The blurred vision can progress to complete blindness, which in some cases can be permanent. None of the other toxins would explain this toxidrome.

### **Quinine toxicity (cinchonism)**

Quinine is a remarkably toxic drug; something which is not so readily acknowledged. It is used as an antimalarial drug and also as a prophylactic agent against leg cramps, although both uses are increasingly falling from vogue due to the availability of better, safer agents. Quinine toxicity, known as cinchonism, may be fatal, usually by cardiac arrhythmia or flash pulmonary oedema in the short term, although incipient renal failure may be fatal more long-term.

Cardiac arrhythmia is a common finding in cinchonism due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively and these rhythms may degenerate into ventricular tachyarrhythmias or fibrillation causing death. Hypoglycaemia is also a common

finding in cinchonism since quinine stimulates pancreatic insulin secretion and this should be corrected rapidly if present. Unlike in the above case, flash pulmonary oedema may develop causing hypoxia and necessitating positive pressure ventilation. Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed and dry skin and abdominal pain.

Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen. In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods. Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.

Management of quinine poisoning is largely supportive with fluids, inotropes and bicarbonate as needed as well as positive pressure ventilation for pulmonary oedema.

#### Question 2 of 89

A 32-year-old male illicit drug user is caught attempting to sell cocaine on the street by the police. On seeing the officers approach him, he swallows a plastic bag containing around 1.5g of cocaine in an attempt to destroy the evidence. The police officers bring the gentleman into the emergency department. He is asymptomatic and complains of no chest pain. His ECG is unremarkable and his admission blood tests demonstrate no abnormalities, including a negative troponin. What should you do next?

[Treat presumptively as acute coronary syndrome5% Discharge the patient to police custody5% Await 12 hour troponin and if negative, discharge to police custody11% Repeat ECG and if no dynamic changes, discharge to police custody7% Monitor the patient until the ingested cocaine is excreted71%](#)

Cocaine produces significant cardiovascular sequelae, classically coronary vasospasm resulting in cardiac ischaemia, presenting as chest pain and similar ECG changes to acute coronary syndrome. Similar vasospasm can lead to transient cerebral ischaemia, resulting in ischaemic infarcts. In addition, cardiac dysrhythmias are also common, including sinus tachycardia, sinus bradycardia, supraventricular tachyarrhythmias, bundle branch block, ventricular fibrillation and torsades de pointes. In this scenario, it is clear that the ingested cocaine has not penetrated to coverings and released systemically. However, the danger remains until the ingested cocaine has been excreted. Patients like this should be monitored for cardiovascular and cerebral sequelae until the ingested amounts are collected.

1. Egred M, Davis GK. Cocaine and the heart. Postgrad Med J 2005; 81: 568-71



## Cocaine

Cocaine is an alkaloid derived from the coca plant. It is widely used as a recreational stimulant. The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem. This increase has made cocaine a favourite topic of question writers.

### Mechanism of action

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

### Cardiovascular effects

- myocardial infarction
- both tachycardia and bradycardia may occur
- hypertension
- QRS widening and QT prolongation
- aortic dissection

### Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia

### Psychiatric effects

- agitation
- psychosis
- hallucinations

### Others

- ischaemic colitis is recognised in patients following cocaine ingestion. This should be considered if patients complain of abdominal pain or rectal bleeding

- hyperthermia
- metabolic acidosis
- rhabdomyolysis

#### Management of cocaine toxicity

- in general benzodiazepines are generally first-line for most cocaine related problems
- chest pain: benzodiazepines + glyceryl trinitrate. If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension: benzodiazepines + sodium nitroprusside
- the use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it

#### Question 3 of 89

A 55-year-old man presents to the Emergency Department after taking an overdose. He can not tell you which of his regular tablets he has taken an overdose of. His past medical history includes Crohn's disease, gastroesophageal reflux disease, hypertension, gout, depression and paroxysmal atrial fibrillation.

He is complaining of chest pain and shortness of breath. Observations - respiratory rate 26/min, saturations 94% on air, heart rate 50/min, blood pressure 75/40 mmHg, temperature 37.2°C.

His ECG shows atrial fibrillation with a broad QRS.

Which drug is the most likely culprit?

[Flecainide28% Amitriptyline46% Allopurinol5% Azathioprine4% Diltiazem18%](#)

Flecainide is the most likely culprit here due to the chest pain, signs of heart failure and prolonged QRS. Diltiazem would be also be possible, but in overdose would likely show a more marked bradycardia with heart block.

Flecainide is a Vaughan Williams Class Ic anti-arrhythmic drug, associated with PR, QRS, and QTc prolongation on the electrocardiogram and development of life-threatening cardiac toxicity in overdose.

The cornerstone of treatment is fluid resuscitation and the administration of magnesium and

sodium bicarbonate. Intravenous fat emulsion has also been trialed with some success.

Note - flecainide should NOT be used in patients who have a structurally abnormal heart due to the risk of causing arrhythmias, including torsades de pointes.

## **Flecainide**

Flecainide is a Vaughan Williams class 1c antiarrhythmic. It slows conduction of the action potential by acting as a potent sodium channel blocker. This may be reflected by widening of the QRS complex and prolongation of the PR interval

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction. The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to increase mortality post myocardial infarction and is therefore contraindicated in this situation

### **Indications**

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

### **Adverse effects**

- negatively inotropic
- bradycardia
- proarrhythmic
- oral paraesthesia
- visual disturbances

### **Question 4 of 89**

A 56-year-old woman with a history of anxiety, depression, and alcoholism is brought to the Emergency department after a mixed overdose. She is known to take tricyclic anti-depressants, benzodiazepines, and codeine phosphate for chronic pain. On examination her Glasgow coma scale is 8, blood pressure is 90/60 mmHg, her respiratory rate is 9 breaths per minute, and she has dilated pupils bilaterally.

Which of the following is the most appropriate next step?

[Airway support49%IV doxapram5%IV flumazenil16%IV naloxone13%IV sodium bicarbonate18%](#)

In patients who are long-term users of tricyclic anti-depressants, particularly in combination with benzodiazepines, rapid reversal of tricyclic effects using flumazenil is not recommended. This is because it may significantly increase the risk of seizures. For this reason, airway support is recommended given the GCS is 8 and the respiratory rate has fallen to 9 breaths per minute.

IV doxapram is a respiratory stimulant used in the management of end-stage COPD where ventilation is not appropriate, Naloxone is used to reverse the effect of opiates, and sodium bicarbonate is used in tricyclic overdose where there is QRS prolongation.

## **Tricyclic overdose**

Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and desipramine (dothiepin) are particularly dangerous in overdose.

Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- arrhythmias
- seizures
- metabolic acidosis
- coma

ECG changes include:

- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

Management

- IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics

#### Question 5 of 89

A 72-year-old male was admitted with 72 hours of progressive ascending motor weakness associated with palpitation and back pain. A diagnosis of Guillain-Barre syndrome was made and he was started on intravenous immunoglobulin (IVIg) with intensive monitoring on the neurology ward. You are asked to review the bloods of the patient on the fourth of five days of IVIg treatment. You note his sodium to have changes as follows: Na 145 → 141 → 134 → 130 → 126. The patient reports 'feeling better after the drip', denies any cough, shortness of breath, diarrhoea, nausea or vomiting. On examination, he appears comfortable in bed, JVP 2/3 cm above the angle of Louis, has warm peripheries and capillary refill time of 2 seconds. His chest is clear on auscultation, cardiovascular examination unremarkable and neurological examination unchanged from admission. What is your management plan?

[No action31%](#)[Intravenous fluid7%](#)[Fluid restrict to 1.5 litres37%](#)[Contact endocrinology team regarding possible syndrome of inappropriate anti-diuretic hormone \(SIADH\)19%](#)[Contact intensive care unit regarding escalation and intubation5%](#)

The patient has received four days of intravenous immunoglobulin (IVIg), which is a protein and hence likely to distort the measurement of sodium, producing a pseudohyponatraemia. This is also observed in patients with high serum concentrations of triglycerides, cholesterol and in those with high serum protein such as myeloma patients. This patient is clinically euvolaemic. No action is required.

### **Immunoglobulins: therapeutics**

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

Uses

- primary and secondary immunodeficiency
- idiopathic thrombocytopenic purpura
- myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- toxic epidermal necrolysis
- pneumonitis induced by CMV following transplantation
- low serum IgG levels following haematopoietic stem cell transplant for malignancy
- dermatomyositis
- chronic inflammatory demyelinating polyradiculopathy

## Basics

- formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- half-life of 3 weeks

## Question 1 of 84

You receive a request for a second opinion from a GP who has performed a general physical check on one of their new patients. He is a 54 year old man who is from Thailand. He had been complaining of low mood, fatigue and sensitivity to the cold. His body mass index is 31 kg/m<sup>2</sup>. The following is a list of investigations performed by the GP.

Na<sup>+</sup> 141 mmol/l  
 K<sup>+</sup> 4.8 mmol/l  
 Urea 9.8 mmol/l  
 Creatinine 142 µmol/l  
 CRP 4 mg/l

Bilirubin 14 µmol/l  
 ALP 86 u/l  
 ALT 27 u/l  
 Calcium 2.89 mmol/l  
 Albumin 39 g/l  
 TSH 24.0 mU/l  
 Free T4 0.8 pmol/l  
 Free T3 0.4 pmol/l

ECG: Heart rate 68, sinus rhythm, QRS width 128ms, flattened T waves V1 to V6

The patient has told the GP that he takes one medication regularly but is unable to give the name. Which medication is most likely to cause the following abnormalities?

[Bendroflumethiazide8% Amiodarone45% Lithium34% Carbimazole8% Propylthiouracil5%](#)

The answer is Lithium. Long term treatments with Lithium causes hypothyroidism in up to a third of patients with middle aged females being the most likely demographic to get this complication. In addition, Lithium therapy is known to cause hypercalcaemia and hyperparathyroidism. Long term lithium therapy is well known to cause renal impairment and weight gain on Lithium is common too. Cardiac side effects are rare on lithium but the most common ECG changes are flattened T waves and a widened QRS complex, in particular a modified Brugada pattern may be seen.

Options D and E can cause hypothyroidism but are not known to cause any of the other abnormalities seen. Option A can cause weight gain and hypercalcaemia but is not known to cause any of the other abnormalities seen. Option B can cause hypothyroidism and similar ECG changes as seen here but is not known to cause any of the other abnormalities.

## **Lithium toxicity**

Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys. Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.

Toxicity may be precipitated by dehydration, renal failure, diuretics (especially bendroflumethiazide), ACE inhibitors, NSAIDs and metronidazole.

Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- seizure
- coma

Management

- mild-moderate toxicity may respond to volume resuscitation with normal saline
- haemodialysis may be needed in severe toxicity
- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion

#### Question 2 of 84

A 35-year-old man was assessed in endocrinology clinic after being referred by his GP for advice on management of the consequences of the patient's use of anabolic steroids. The patient reported that he had been using anabolic steroids intermittently for the previous 10 years to augment his weight-training regime. Having recently become aware of the potential adverse health consequences, the patient now wished to know how he could safely stop his anabolic steroid use.

The patient described his pattern of anabolic steroid use: typically, he had been taking a 'cycle' of one or more oral synthetic testosterone derivatives for between 6-12 weeks, prior to a 3-4 week break in his use of steroids. The patient stated this strategy was an attempt to minimise his risk of side effects. The patient had not received any medical supervision of his anabolic steroid use, relying instead on discussions with friends at his gym and information from online forums. The patient declined to disclose the source from which he had obtained his supply of medications.

The patient stated that he believed his anabolic steroid use had contributed to his male pattern baldness and also had caused intermittent breakouts of acne on his chest and face. The patient was not aware of any other symptoms related to his steroid use, although stated that he was concerned about possible lasting cardiac side effects. The patient had no other significant medical history and took no other regular medications. He did not consume cigarettes, alcohol or recreational drugs.

General examination of the patient revealed a muscular and lean adult male in apparent good health. A cardiovascular system examination noted a forceful but not displaced apex beat. Mild gynaecomastia was present but gastrointestinal examination was otherwise unremarkable. Using an orchidometer the patient's testicular volume was estimated as 16 ml. Although anxious about the possible health consequences of his anabolic steroid use, the patient did not seem to be significantly depressed or anxious.

Haemoglobin	173 g / dL
Sodium	148 mmol / L
Potassium	3.6 mmol / L
Alkaline phosphatase	135 U / L (reference 35-100)
ALT	32 U / L (reference 3-36)
Bilirubin	20 micromol / L (reference < 26)



Prolactin	469 mU / L (reference 80 - 400)
Luteinising hormone	0.9 IU / L (reference 1.8 - 8.6)
Follicle-stimulating hormone	1.2 mU / ml (reference 1.5 - 12.4)
Fasting LDL cholesterol	4.1 mmol / L (reference < 3.0)
Fasting HDL cholesterol	1.0 mmol / L (reference > 1.2)
HbA1C	45 mmol / mol (reference < 42)

What is the appropriate advice to the patient regarding the safe cessation of anabolic steroid use?

[Convert patient to prescribed testosterone replacement and taper over 1 year19%](#)  
[Taper anabolic steroid use over period of 6 months14%](#)  
[Stop immediately, tapered withdrawal not required38%](#)  
[Taper anabolic steroid use over period of 6 weeks24%](#)  
[Convert patient to prescribed testosterone replacement and continue lifelong4%](#)

The patient has typical side effects and examination findings associated with long-standing anabolic steroid use. These include male pattern baldness, acne, gynaecomastia and testicular atrophy (typical adult male testicular volume around 25 mL). His blood tests also demonstrate typical abnormalities including erythropoiesis, hypernatraemia, hypokalaemia, cholestatic liver function tests, deranged lipid profile, evidence of elevated serum glucose and typical hormone profile abnormalities.

## **Anabolic steroid use**

Anabolic steroid use is associated with several serious long-term health consequences. Cardiac morbidity and mortality are increased by anabolic steroid use, although the precise mechanism of this effect is unclear. Hepatic side effects also occur secondary to chronic vascular injury: these include hepatocellular carcinoma and hepatic adenoma. Psychiatric illness is also commonly co-morbid with anabolic steroid use. Additionally, users who inject anabolic steroids have an increased risk of blood-borne viruses if needles are shared between individuals.

Due to the above concerns, patients should be strongly counselled to stop using anabolic steroids. There is no requirement for tapering of doses. Many of the above blood test abnormalities

normalise once anabolic steroid consumption ceases. The expert recommendation is for lifelong monitoring for potential complications, initially annually with frequency reducing once blood markers normalise and in the absence of apparent adverse effects.

Brooks J, Ahmad I, Easton G. Anabolic steroid use. BMJ 2016;353:i5023.

#### Question 3 of 84

A 49-year-old woman with a diagnosis of Hashimoto's thyroiditis is seen in clinic with recurrence of lethargy, constipation, cold intolerance and pedal oedema. These symptoms had previously resolved on starting treatment with levothyroxine.

Her co-morbidities include type 2 diabetes mellitus and hypertension. She was also diagnosed with mycobacterium tuberculosis of the lung five months ago. Her current medications are levothyroxine, amlodipine, ramipril, metformin, gliclazide, rifampicin, isoniazid and pyridoxine.

Her temperature is 36.5°C, pulse 55 beats per minute, blood pressure 165/102 mmHg and respiratory rate 15 breaths per minute.

Thyroid function tests showed:

Free thyroxine (T4)	5 pmol/L (10-25)
Free triiodothyronine (T3)	3 pmol/L (5-10)
Thyroid-stimulating hormone	7.2 mU/L (0.4-5.0)

What is the likely cause of her symptoms?

[Vitamin B6 deficiency7%](#)[Rifampicin53%](#)[Isoniazid14%](#)[Non-compliance with medications20%](#)[Amlodipine6%](#)

In patients with treated hypothyroidism, thyroxine requirements are increased by cytochrome P450 inducing drugs such as rifampicin. Isoniazid does not have this effect.

Non-compliance with levothyroxine may also give a similar picture, but there is no firm evidence to suggest that this is the case, especially as the patient's symptoms had previously resolved.

Amlodipine can cause peripheral oedema, but it would not account for the other symptoms and investigation results.

Pyridoxine is a form of vitamin B6. Isoniazid interferes competitively with pyridoxine metabolism. However, a deficiency would typically present with a peripheral neuropathy.

### **P450 enzyme system**

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inducers of the P450 system include

- antiepileptics: phenytoin, carbamazepine
- barbiturates: phenobarbitone
- rifampicin
- St John's Wort
- chronic alcohol intake
- griseofulvin
- smoking (affects CYP1A2, reason why smokers require more aminophylline)

Inhibitors of the P450 system include

- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- cimetidine, omeprazole
- amiodarone
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- ritonavir
- sodium valproate
- acute alcohol intake
- quinupristin

Question 1 of 81

A 26 year old male is admitted to hospital with difficulty in breathing, wheeze and a cough productive of green sputum. He is assessed and determined to have a community acquired lower

respiratory tract infection with biochemical and radiological evidence lending weight to this diagnosis. His medical history is significant for capricious asthma and he has been admitted to intensive care previously and ventilated. Currently he is taking salbutamol and formoterol/budesonide inhalers at their maximum doses, montelukast, aminophylline and omalizumab (Xolair) monthly subcutaneous injections.

Which of the following antibiotics is best avoided in this patient's treatment?

[Amoxicillin 7% Azithromycin 30% Ciprofloxacin 41% Doxycycline 9% Gentamicin 13%](#)

Co-administration of aminophylline and ciprofloxacin can cause significant toxicity and should be avoided.

This question is about drugs which interact via their effect on hepatic cytochrome metabolising enzymes. Pharmacokinetically speaking, any drug has the potential to affect how another is processed, metabolised or excreted but only some have a relevant clinical effect.

In the above vignette we are concerned about a newly commenced antibiotic affecting one of the patient's regular medications and causing a deleterious effect. Salbutamol and formoterol are beta agonist drugs which have their own side effects of adrenergic updrive but they rarely have any clinically relevant interactions. Similarly, the inhaled steroid budesonide is seldom affected by other co-administered drugs to a vast degree. Omalizumab is a monoclonal antibody to unbound human IgE and is used as an adjunct treatment in atopic asthma in steroid resistant patients who display extreme histamine sensitivity and elevated IgE levels. It has few clinical interactions. Aminophylline derivatives are moderately active bronchodilators which work two-fold; by inhibiting phosphodiesterases and hence ultimately dampening inflammatory cytokines, and also by acting as an antagonist at adenosine receptors in the heart, brain and lung. It is metabolised extensively by the liver, predominantly by the enzyme 1A2 and has a narrow therapeutic window with elimination pathways becoming saturated even at therapeutic doses. Any drug which inhibits cytochrome enzyme 1A2 can rapidly lead to aminophylline toxicity.

Ciprofloxacin in particular, is a strong inhibitor of enzyme 1A2 causing a decrease in function of at least 80% and an average rise in serum concentrations of metabolising substrate of five-fold. Co-administration of ciprofloxacin with aminophylline is extremely likely to cause toxicity.

The use of macrolide antibiotics with aminophylline is contentious. Most macrolides actually induce activity of 1A2 leading to a reduction in aminophylline levels (similar to the effect of long term smoking). Both aminophylline and macrolide antibiotics however tend to predispose to prolongation of myocardial repolarisation time and there is a risk of ventricular arrhythmia. Azithromycin only poses a theoretical risk rather than an observed one and dose reduction and drug monitoring of aminophylline levels is appropriate if the two drugs must be used together. Erythromycin is best avoided.

Doxycycline use with aminophylline can cause theoretical fluctuations in serum aminophylline levels but regular monitoring of drug levels is sufficient to avoid toxicity. Neither amoxicillin nor gentamicin have clinically relevant drug interactions with aminophylline.

## Question 2 of 81

You are asked to review a 44-year-old lady in the emergency department. She is well known to the mental health liaison team because of her multiple suicide attempts. She is agitated and slightly confused and unable to give a precise history. She is able to tell you that she can't see clearly and has a dry mouth.

Her sister explains that the patient has been prescribed medicines for chronic neuropathic back pain and has taken them all after splitting up with her boyfriend.

On examination she has symmetrically dilated pupils but no focal motor deficit. Her heart sounds are normal and her lung fields are clear on auscultation. An ECG shows sinus tachycardia with a QRS of 170.

Bloods results are as follows:

Hb	125 g/l
Platelets	$440 \times 10^9/l$
WBC	$9.9 \times 10^9/l$
Na <sup>+</sup>	135 mmol/l
K <sup>+</sup>	4.2 mmol/l
Urea	5.1 mmol/l
Creatinine	88 $\mu$ mol/l
Plasma Paracetamol	<5mmol/l

You request an arterial blood gas which shows the following readings:

pH 7.29  
pCO<sub>2</sub> 3.4 kPa  
pO<sub>2</sub> 14.5 kPa

What is the most appropriate next step in this patient's management?

[IV sodium bicarbonate79%Haemodialysis7%IV lignocaine6%IV amiodarone4%Naloxone4%](#)

The culprit here is a tricyclic antidepressant, such as dosulepin or amitriptyline. The first step in treating this patient is to reverse the metabolic acidosis with IV bicarbonate. Dialysis is of no benefit in this scenario.

The dilated pupils and absence of respiratory depression point away from opioid overdose, making naloxone the wrong answer.

## Tricyclic overdose

Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and doxepin (dothiepin) are particularly dangerous in overdose.

Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- arrhythmias
- seizures
- metabolic acidosis
- coma

ECG changes include:

- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS  $> 100\text{ms}$  is associated with an increased risk of seizures whilst QRS  $> 160\text{ms}$  is associated with ventricular arrhythmias

## Management

- IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics

### Question 3 of 81

A 22-year-old man is admitted to the Emergency Department with palpitations. Earlier in the evening he snorted a large amount of cocaine and has been feeling unwell since. His heart rate is 148/min, blood pressure 135/78 mmHg and oxygen saturations 99% on room air. The ECG shows sinus tachycardia with no ischaemic changes. He is given intravenous diazepam but this fails to settle his symptoms. What is the most appropriate next step?

[Sotalol12%](#) [Bisoprolol34%](#) [Verapamil41%](#) [Digoxin5%](#) [Ivabradine8%](#)

Cocaine toxicity - avoid beta-blockers

Firstly this question highlights the importance of benzodiazepines in the management of cocaine toxicity. Pretty much any complication of cocaine use is initially treated with benzodiazepines. As this has already been given we have to move to next line treatments.

Beta-blockers should be avoided in cocaine toxicity due to the risk of coronary vasospasm (see below). The most appropriate treatment is therefore verapamil.

## Cocaine

Cocaine is an alkaloid derived from the coca plant. It is widely used as a recreational stimulant. The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem. This increase has made cocaine a favourite topic of question writers.

Mechanism of action

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

Cardiovascular effects

- myocardial infarction
- both tachycardia and bradycardia may occur
- hypertension
- QRS widening and QT prolongation
- aortic dissection

## Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia

## Psychiatric effects

- agitation
- psychosis
- hallucinations

## Others

- ischaemic colitis is recognised in patients following cocaine ingestion. This should be considered if patients complain of abdominal pain or rectal bleeding
- hyperthermia
- metabolic acidosis
- rhabdomyolysis

## Management of cocaine toxicity

- in general benzodiazepines are generally first-line for most cocaine related problems
- chest pain: benzodiazepines + glyceryl trinitrate. If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension: benzodiazepines + sodium nitroprusside
- the use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it

## Question 4 of 81

A 22-year-old male is 'blue-lighted' to the Emergency Department having been found collapsed at a party. On arrival, his GCS is 3/15 and he is immediately intubated and ventilated by the Emergency Physicians.



On examination he is afebrile. He is mildly bradycardic at 53bpm and his blood pressure is 109/69mmHg. His pupils measure 2mm bilaterally. IV access is obtained and 400 micrograms of naloxone are administered without effect. The on-call radiologist is contacted and a CT head scan is arranged.

One hour later the patient extubates himself without warning. He is referred to medicine as his GCS is still 13/15. His CT demonstrates no acute intracranial pathology. By the time you arrive in the Emergency Department his GCS has improved to 15/15 and he is demanding to go home.

Which drug is most likely to be implicated?

[Diazepam 11% Methoxetamine 10% Gamma-hydroxybutyric acid \(GHB\) 49% Heroin 17% Methamphetamine 13%](#)

GHB or 'Grievous Bodily Harm' is a colourless, odourless, bitter-tasting substance that acts as a CNS depressant. It is abused for its ability to induce euphoria, amnesia, and hypnosis. It is popular amongst party-goers and achieved notoriety for its use as a date-rape drug.

GHB toxicity occurs secondary to its effects as a CNS depressant. Patients typically present with coma, respiratory depression, mild bradycardia, and vomiting. The key feature of GHB toxicity is its short recovery time. Patients typically recover in 6 hours and toxicity is often maximal on presentation. Recovery often occurs spontaneously in the Emergency Department and patients have been known to self-extubate.

Heroin and diazepam could both produce a similar toxidrome. Recovery is generally more gradual, and one would expect naloxone to reverse a heroin overdose.

Methamphetamine is a stimulant. Clinical features include agitation, tachycardia, hypertension, mydriasis, and hyperthermia.

Methoxetamine is an analogue of the dissociative anaesthetics ketamine and phencyclidine (PCP). In addition to dissociative phenomena, it also causes tachycardia, hypertension, confusion, and mydriasis. Patients may also present with an acute cerebellar syndrome.

## **Novel psychoactive substances**

Novel psychoactive substances is the medical term for the many new substances which are chemically related to established recreational drugs such as MDMA and cannabis. They are often referred to as 'legal highs' although this is a misnomer in the UK, as their distribution and sale have been illegal since 2016.

The information below describes some of the common types:

### Stimulants

- similar to MDMA, amphetamines and cocaine, resulting in increased levels of serotonin, dopamine and noradrenaline, resulting in a 'high' and feeling of euphoria
- a common example is a stimulant NPS is mephedrone ('bath salts', 'M-CAT', 'meow meow'). It is a cathinone and structurally similar to khat, a plant found in East Africa
- another example is benzylpiperazine ('Exodus', 'Legal X', 'Legal E')
- typically swallowed as a pill/powder ('bombing') or snorted
- adverse effect profile similar to MDMA/cocaine, with the risk of serotonin syndrome

### Cannabinoids

- termed synthetic cannabinoid receptor agonists
- commonly referred to as 'spice'
- typically sprayed on to herbal mixtures which are then smoked. Also available in liquid form which is then inhaled using e-cigarettes
- similar adverse effects to cannabis

### Hallucinogenics

- can be either dissociatives and psychedelics
- dissociatives produce a similar effect to ketamine, with a sense of not being connected to the physical body or time. A common dissociative NPS is methoxetamine ('mexxy')
- psychedelics have a similar effect to LSD although NPS versions may also be a stimulant

### Depressant

- can be either opioid or benzodiazepine-based
- usually taken as a pill or a powder
- often structurally very similar to the original drug class, hence the adverse effects are similar
- benzodiazepine NPS often have a significantly longer half-life

### Other substances include:

- Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL): 'G', 'Geebs' or 'Liquid Ecstasy'
- Nitrous oxide: 'Hippie crack'

### Question 5 of 81

A 76-year-old man presented with shortness of breath to the emergency department. On the basis of a recent knee replacement operation and unremarkable chest x-ray a CT pulmonary angiogram was performed and demonstrated a segmental pulmonary embolus with evidence of mild right heart strain. The patient was haemodynamically stable and required only minimal supplemental oxygen therapy.

The patient had known chronic kidney disease stage IV secondary to type 2 diabetes and hypertension. Treatment was therefore initiated with an intravenous unfractionated heparin infusion.

The patient's condition was stable over the following week with warfarin loading cautiously started at day 6 of admission. Routine blood tests at this point indicated a new abnormality in full blood count leading to further investigations as detailed below.

Haemoglobin	14.5 g / dL
White blood cells	$8.6 \times 10^3$ / microlitre
Neutrophils	$4.5 \times 10^3$ / microlitre
Lymphocytes	$2.1 \times 10^3$ / microlitre
Platelets	$67 \times 10^3$ / microlitre
Mean cell volume	85 fL
Mean cell haemoglobin	30.1 pg
B12	252 pmol / L
Folate	20 nmol / L

Heparin induced thrombocytopenia antibodies: positive (high titre)

Following cessation of IV heparin infusion, what is the appropriate management of the patient's thrombocytopenia?

[Bivalirudin 59%](#) [Enoxaparin 7%](#) [Warfarin 9%](#) [Tirofiban 17%](#) [Platelet transfusion 7%](#)

This patient has a confirmed diagnosis of heparin induced thrombocytopenia (HIT) based on the suggestive clinical picture and positive HIT antibody screen. Decision tools such as the Warkentin probability scale can be useful by providing a pre-test probability score of HIT based on the clinical picture. In this case, the timing of thrombocytopenia with onset between 5-10 days after initial exposure to heparin is highly suggestive.

In suspected or confirmed cases of HIT, heparin anticoagulants must be withheld immediately. Treatment with a non-heparin anticoagulant such as bivalirudin should be started to reduce the risk of HIT-related thrombosis.

Vitamin K antagonists such as warfarin such be withheld or reversed as they do not prevent HIT-

associated thrombosis and increase the risk of venous gangrene. Platelet transfusion would not be indicated in this patient.

Linkins L-A. Heparin induced thrombocytopenia. BMJ 2014;349:7566.

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	<b>Standard heparin</b>	<b>Low molecular weight heparin (LMWH)</b>
<b>Administration</b>	Intravenous	Subcutaneous
<b>Duration of action</b>	Short	Long
<b>Mechanism of action</b>	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
<b>Side-effects</b>	Bleeding Heparin-induced thrombocytopenia (HIT) Osteoporosis	Bleeding Lower risk of HIT and osteoporosis with LMWH
<b>Monitoring</b>	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
<b>Notes</b>	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

### Heparin-induced thrombocytopenia (HIT)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment

- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

#### Question 1 of 75

A 50 year-old man presents to the medical assessment unit with a two day history of nausea and vomiting. His notes are currently not available to you, and the patient is unable to recall his medical problems. He is currently an inpatient at the local psychiatry facility.

On examination, he appears drowsy with an ataxic gait. Neurological examination reveals normal tone with generalised reduced power. He also has a coarse tremor when his hands are outstretched.

Cardiorespiratory examination reveals is unremarkable.

ECG- sinus arrhythmia at 90 beats per minute. T wave inversion in leads V1-V3.

#### Observations

Blood pressure- 150/90 mmHg

Heart rate- 90 beats per minute

Respiratory rate- 16 breaths per minute

Oxygen saturations- 99% on room air

Temperature- 37.3°C

What is the most likely cause of his symptoms?

[Lithium toxicity68% Alcohol withdrawal10% Serotonin syndrome9% Neuroleptic malignant syndrome6% Tricyclic antidepressant overdose7%](#)

Lithium salts are used in the prophylaxis and treatment of bipolar disorder, refractory depression and aggressive or self-harming behaviour.

Lithium has a narrow therapeutic range (0.5-1 mmol/l). The likelihood of toxicity increases with increasing serum lithium levels. Toxic effects are seen with a concentration of >2 mmol/l.

Very early features may be non-specific, such as apathy and restlessness

Early signs of toxicity (1-2 mmol/l)

- anorexia and vomiting
- ataxia and dysarthria
- nystagmus
- blurred vision
- coarse tremor
- drowsiness

Late signs of toxicity (>2mmol/l)

- coma
- seizures
- acute renal failure
- death

Serotonin syndrome is a drug reaction to serotonergic agents, and ranges from mild to severe. It is characterised by a triad of autonomic hyperactivity (hyperthermia, tachycardia), neuromuscular abnormality (tremor) and mental state changes (confusion, coma).

Neuroleptic malignant syndrome is a rare reaction to neuroleptic drugs, often following initiation or increase in dose. It is characterised by recent neuroleptic use, hyperthermia, rigidity and autonomic dysfunction.

## **Lithium toxicity**

Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys. Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.

Toxicity may be precipitated by dehydration, renal failure, diuretics (especially bendroflumethiazide), ACE inhibitors, NSAIDs and metronidazole.

Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)

- hyperreflexia
- acute confusion
- seizure
- coma

## Management

- mild-moderate toxicity may respond to volume resuscitation with normal saline
- haemodialysis may be needed in severe toxicity
- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion

## Question 3 of 75

A 33 year female of Arabic descent with bullous pemphigus is admitted electively for intravenous immunoglobulins. She has no other past medical history, no recent travel history and has lived in rural Norfolk her whole life. On day 4 of a 5 day planned course of treatment, she develops pyrexia, nausea and vomiting. On examination, you note mild neck stiffness and photophobia. She also complains of a posterior headache. Her serum markers are as below:

WBC  $14.0 \times 10^9/l$

Neuts  $11.0 \times 10^9/l$

Na<sup>+</sup> 133 mmol/l

K<sup>+</sup> 3.8 mmol/l

Urea 4.7 mmol/l

Creatinine 80  $\mu$ mol/l

CRP 4 mg/l

A CT head is unremarkable. The immunoglobulin is stopped. You perform a lumbar puncture: WCC 10/mm<sup>3</sup>, protein 0.4g/L, no organisms, opening pressure 17.8 cm H<sub>2</sub>O. Blood cultures taken during a temperature spike grow no organisms after 48 hours. What is the diagnosis?

[Aseptic meningitis 65% Bullous pemphigus flare 8% TB reactivation, resulting in TB meningitis 1% Viral meningitis 12% Bacterial meningitis 5%](#)

Aseptic meningitis is a classic complication of IVIg treatment. This patient's inflammatory markers are unremarkable, as is the rest of her septic screen. There is little to suggest worsening of underlying bullous pemphigus. Aseptic meningitis occurs in 1% of patients with intravenous immunoglobulin. The key is to rule out any infective causes and to stop the immunoglobulin.

treatment until this is been done. Modern preparations can be stored in a fridge for months: there does not need to be fears that expensive IVIg will be wasted if you dont continue with the treatment!

## **Immunoglobulins: therapeutics**

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

### Uses

- primary and secondary immunodeficiency
- idiopathic thrombocytopenic purpura
- myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- toxic epidermal necrolysis
- pneumonitis induced by CMV following transplantation
- low serum IgG levels following haematopoietic stem cell transplant for malignancy
- dermatomyositis
- chronic inflammatory demyelinating polyradiculopathy

### Basics

- formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- half-life of 3 weeks

### Question 4 of 75

A 48-year-old man is referred to the outpatient department by his GP, having experienced tremor, heat intolerance and 2 kg weight loss over the last 6 weeks. His past medical history includes having atrial fibrillation for which he takes warfarin and amiodarone. He is a non-smoker and drinks on average 10 units of alcohol per week.

Blood tests are performed and reveal:



Hb	142 g/l
Platelets	220 * 10 <sup>9</sup> /l
WBC	7.2 * 10 <sup>9</sup> /l
Na <sup>+</sup>	140 mmol/l
K <sup>+</sup>	4.2 mmol/l
Urea	4.5 mmol/l
Creatinine	45 µmol/l
Thyroid stimulating hormone (TSH)	0.03 mu/l
Free thyroxine (T4)	29 pmol/l
Total T3 (TT3)	252 ng/dL    Normal range 75 -200 ng/dL

A colour flow Doppler sonography of the thyroid is performed and shows absent vascularity and gland destruction.

What is the most likely diagnosis?

[Type 1 amiodarone-induced thyrotoxicosis24%](#) [Type 2 amiodarone-induced thyrotoxicosis63%](#) [Grave's disease4%](#) [Hashimotos thyroiditis4%](#) [De Quervains thyroiditis5%](#)

Type 2 amiodarone-induced thyrotoxicosis typically occurs in patients without underlying thyroid disease and is the result of the toxic effect of amiodarone on the thyroid follicular cells, causing a destructive thyroiditis that results in excess release of preformed T4 and T3 into the circulation. The condition has two phases a thyrotoxic phase which can last weeks to months, which is often followed by a hypothyroid phase and an eventual recovery in most patients.

Type 1 amiodarone-induced thyrotoxicosis normally occurs in patients with underlying thyroid pathology like Graves disease. In these patients, there is accelerated thyroid hormone synthesis secondary to the iodide load from the amiodarone therapy.

## **Amiodarone and the thyroid gland**

Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

### **Amiodarone-induced hypothyroidism**

The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect\*

Amiodarone may be continued if this is desirable

### **Amiodarone-induced thyrotoxicosis**

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

	<b>AIT type 1</b>	<b>AIT type 2</b>
Pathophysiology	Excess iodine-induced thyroid hormone synthesis	Amiodarone-related destructive thyroiditis
Goitre	Present	Absent
Management	Carbimazole or potassium perchlorate	Corticosteroids

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT

\*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

### **Question 5 of 75**

A 70-year-old man is admitted to hospital with shortness of breath and a productive cough. Following initial investigation a community-acquired pneumonia is diagnosed and treatment with IV fluids and IV antibiotics initiated promptly. Subcutaneous enoxaparin for venous thromboprophylaxis was initiated on the day of admission. Due to persistent hypotension and oliguria secondary due to presumed septic shock, the patient was admitted to the General Intensive Care Unit for inotropic support around 12 hours after initial presentation.

The patients past medical history featured a previous ST elevation myocardial infarction, treated with primary percutaneous coronary interventions one year previously. Regular medications included Aspirin, Clopidogrel, Ramipril, Bisoprolol and Atorvastatin. The patient had no known drug allergies and lived independently in a house with his wife.

With the above management, the patients condition stabilised and he was discharged to a respiratory ward on day 3 of the admission. Routine blood tests taken on day 7 of admission demonstrated a marked fall in platelet count compared to admission bloods. Full examination of the patient at this time did not demonstrate any evidence of venous thrombosis with no skin changes. Following advice from haematology further investigations were requested as detailed below.

Blood results	Day 0 (admission)	Day 3	Day 7
Platelets (x 10 <sup>3</sup> / microlitre)	189	156	87
International normalised ratio	1.1	1.3	1.2

Heparin induced thrombocytopenia antibodies: positive (moderate titre)

What further investigation is required (if any) to confirm a diagnosis of heparin induced thrombocytopenia?

[Serotonin release assay26%Repeat heparin induced thrombocytopenia antibodies10% Venous doppler ultrasound of lower limbs5%Fibrinogen break-down products14%No further investigation required46%](#)

The diagnosis of heparin induced thrombocytopenia is based on the correlation of the clinical presentation and laboratory results. It is helpful to calculate a pre-test probability score using a tool such as the Warkentin probability scale to assist with interpretation of HIT antibody results. In this case the patient has an intermediate clinical probability of HIT based on the fall in platelet count > 50 % of baseline between day 5-10 of initiating heparin therapy. However, the presence of an alternative cause of thrombocytopenia (severe sepsis) reduces the probability of HIT.

The combination of moderate clinical probability and moderate HIT antibody titre indicate the need for additional testing. Functional assays such as the serotonin release assay have a high sensitivity and specificity for HIT (> 95 %) and so will confirm or exclude a diagnosis of HIT.

Given the clinical picture, it would be prudent in this case to hold further heparin anticoagulants and introduce a non-heparin anticoagulant such as Bivalirudin to reduce the risk of HIT related thrombosis while further testing is being conducted.

Linkins L-A. Heparin induced thrombocytopenia. BMJ 2014;349:7566.

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	Standard heparin	Low molecular weight heparin (LMWH)
<b>Administration</b>	Intravenous	Subcutaneous
<b>Duration of action</b>	Short	Long

	<b>Standard heparin</b>	<b>Low molecular weight heparin (LMWH)</b>
<b>Mechanism of action</b>	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, Xa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
<b>Side-effects</b>	Bleeding Heparin-induced thrombocytopenia (HIT) Osteoporosis	Bleeding Lower risk of HIT and osteoporosis with LMWH
<b>Monitoring</b>	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
<b>Notes</b>	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

#### Heparin-induced thrombocytopenia (HIT)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

#### Question 6 of 75

A 65-year-old female presents to respiratory outpatients with an 8-week history of gradually worsening shortness of breath. Her exercise tolerance has reduced to 50 yards from several miles; she reports chronic lower back pain but no other symptoms. Her past medical history includes type 2 diabetes mellitus, psoriasis, recurrent urinary tract infections and ischaemic heart disease. She currently takes metformin 500 mg BD, bisoprolol 2.5 mg OD, aspirin 75 mg OD, atorvastatin 40 mg ON, ramipril 2.5 mg and nitrofurantoin 50 mg ON with no change in the last

6 months. She has never smoked, has no pets and works as a secretary. On examination, the patient is breathless on minimal exertion. Observations are normal, there is no clubbing and she has fine end-inspiratory crepitations at both bases. A CT chest shows ground glass changes with minimal honey combing at both bases. What is the most likely cause of her underlying respiratory condition?

[Asbestosis9%Psoriasis8%Metformin4%Ankylosing spondylitis15%Nitrofurantoin64%](#)

This patient has a history and examination consistent with pulmonary fibrosis. Her CT chest supports this demonstrating ground glass and honey combing at both bases. Pulmonary function tests will demonstrate a restrictive pattern and arterial blood gas analysis will show a type 1 respiratory failure. Long-term use of nitrofurantoin is known to cause a basal pattern of pulmonary fibrosis and is the most likely culprit in this case. There is no suggestion of asbestos exposure in the history and both psoriasis and ankylosing spondylitis classically cause an apical pattern of fibrosis. Lower back pain is a common medical complaint in this age group and ankylosing spondylitis tends to present in younger males.

## **Drugs causing lung fibrosis**

### **Causes**

- amiodarone
- cytotoxic agents: busulphan, bleomycin
- anti-rheumatoid drugs: methotrexate, sulfasalazine, gold
- nitrofurantoin
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide)

### **Question 1 of 69**

You are asked to review a 75-year-old lady on the surgical ward. She has malignant carcinoma of the colon and had a large bowel resection seven days ago. Despite being on dalteparin since admission, she had developed a right-sided deep venous thrombosis (DVT). She tells you she had a similar problem ten years ago and had to take 'blood-thinning injections' for several months.

On examination she looks well with no signs of respiratory distress. Her oxygen saturations are 99% on room air and on auscultation she has vesicular breath sounds throughout both lung fields.

Her pre-operative blood tests are as following:

Hb	119 g/l	Na <sup>+</sup>	135 mmol/l	Bilirubin	12 mol/l
Platelets	457 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.5 mmol/l	ALP	111 u/l
WBC	6.8 * 10 <sup>9</sup> /l	Urea	4.9 mmol/l	ALT	45 u/l
Neuts	4.0 * 10 <sup>9</sup> /l	Creatinine	81 µmol/l	γGT	30 u/l
Lymphs	0.9 * 10 <sup>9</sup> /l			Albumin	34 g/l
Eosin	0.0 * 10 <sup>9</sup> /l				

Her blood results today are as follows:

Hb	105 g/l	Na <sup>+</sup>	133 mmol/l	Prothrombin time	10.7 s
Platelets	77 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.1 mmol/l	APTT	27.5s
WBC	7.6 * 10 <sup>9</sup> /l	Urea	5.7 mmol/l	APTT ratio	45 u/l
Neuts	4.9 * 10 <sup>9</sup> /l	Creatinine	98 µmol/l	D-Dimer	>1000 ng/ml
Lymphs	1.1 * 10 <sup>9</sup> /l			Albumin	31 g/l
Eosin	0.1 * 10 <sup>9</sup> /l				

Which of the following represents the optimal management for this patient whilst she remains an inpatient?

[Warfarin8% Bivalirudin58% IV heparin infusion16% Plasma exchange7% Rivaroxaban11%](#)

This lady has heparin-induced thrombocytopenia (HIT). She needs anticoagulation but should ideally be switched to a non-heparin drug for now. Bivalirudin is a direct thrombin inhibitor and is not associated with HIT.

Plasma exchange would be the treatment of choice for thrombotic thrombocytopenic purpura, which is not the case here.

Warfarin causes a rapid fall in protein C levels, risking complications such as skin necrosis, so is not used acutely.

## Heparin

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Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

### Question 3 of 69

A 30-year-old man was brought in after being found unconscious in a club by his friends. His friends report he may have taken some 'Ecstasy' pills in the club but were unsure how many, and he was confused and agitated prior to being found in the toilet unconscious. His past medical history includes depression, for which he was taking fluoxetine 40mg daily.

On examination, he was drowsy, with a temperature of 39°C, heart rate of 120bpm, respiratory rate of 22 breaths per minute, oxygen saturation of 96% on air, and a blood pressure of 160/98mmHg. He was sweating and had a tremor in his arms. Pupils were dilated, equal and reactive to light. He was hypertonic and hyper-reflexic in his arms and legs.

### Investigations

Na+	136 mmol/l
K+	4.6 mmol/l
Urea	10.9 mmol/l
Creatinine	90 µmol/l
Creatine kinase	274 IU/L
Serum bilirubin	14 µmol/l
Serum alkaline phosphatase	105 IU/l
Serum aspartate aminotransferase	20 IU/l
C-Reactive protein	2 mg/l
Haemoglobin	146 g/l
White cell count	6.6 x 10 <sup>9</sup> /L
INR	1.1

Intravenous fluids were started and a bolus dose of Lorazepam was given. What other medication may be useful to manage this patient?

[Dantrolene58%](#) [Buspirone5%](#) [Procyclidine22%](#) [Dextromethorphan7%](#) [Phenelzine8%](#)

This patient has malignant hyperthermia secondary to serotonin syndrome, likely precipitated by taking Ecstasy (3,4-methylenedioxy-N-methylamphetamine, or MDMA) along with his usual fluoxetine, a selective serotonin reuptake inhibitor (SSRI).

Other risk factors include:

- Antidepressants- monoamine-oxidase inhibitors (MAOI), tricyclic antidepressants
- Analgesia- tramadol, dextromethorphan
- Anti-emetics- ondansetron, metoclopramide
- Amphetamines (and other recreational drugs): amphetamines, cocaine, LSD
- Others: Buspirone, linezolid



The treatment of serotonin syndrome is supportive, with intravenous fluids, and benzodiazepines for agitation. Hyperthermia can be treated with cyproheptadine, dantrolene or chlorpromazine. Untreated hyperthermia can lead to rhabdomyolysis and renal failure, and if the temperature is above 40°C these patients should be paralysed and ventilated with a trial of ice baths or ice packs if necessary.

Buspirone, Dextromethorphan, Phenelzine (a MAOI) are all risk factors for serotonin syndrome.

Procyclidine is used in the treatment of acute dystonias and drug-induced extrapyramidal symptoms.

## **Malignant hyperthermia**

### Overview

- condition often seen following administration of anaesthetic agents
- characterised by hyperpyrexia and muscle rigidity
- cause by excessive release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum of skeletal muscle
- associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

### Causative agents

- halothane
- suxamethonium
- other drugs: antipsychotics (neuroleptic malignant syndrome)

### Investigations

- CK raised
- contracture tests with halothane and caffeine

### Management

- dantrolene - prevents  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum

Question 5 of 69

A 47-year-old man is admitted to the Medical Assessment Unit with a pneumonia. He has had a cough for the last week which has not settled with amoxicillin from his GP.

His past medical history includes alcoholic liver disease with a hepatic transplant 6 months previously, hypertension and diet-controlled type II diabetes. He has remained abstinent from alcohol for the last 18 months and is a lifelong non-smoker. His medications are ramipril, simvastatin and tacrolimus.

On admission he has a temperature of 38.1 °C and oxygen saturations of 94% on air. His heart rate is 110 beats per minute and blood pressure is 105/65 mmHg. On auscultation he has left basal crepitations and chest x-ray confirms a left lower lobe pneumonia.

He is started on intravenous fluids, 2 litres oxygen via nasal cannulae, co-amoxiclav and clarithromycin. His statin is withheld.

2 days later, the ward team are asked to review the patient as he has developed limb twitching. During the assessment he has a generalised tonic-clonic seizure which requires lorazepam to terminate it.

Which investigation is most likely to reveal the cause for his seizures?

[Blood cultures5%](#) [CT head8%](#) [Electrolytes19%](#) [Lumbar puncture7%](#) [Tacrolimus level62%](#)

The first issue to consider in this question is whether this gentleman's seizure is most likely to be related to infection or metabolic disturbance.

Given that it is two days following his admission with infection, it is unlikely that he has an undetected meningitis, as he would likely have exhibited other symptoms and become much more unwell in this time.

A CT head would be done prior to a lumbar puncture but would not confirm a diagnosis of meningitis, and this gentleman is unlikely to have a new intracranial pathology given the history. Although febrile seizures are a possibility, they are unusual in adults, and again would be uncommon after 2 days of appropriate antibiotics.

Although blood cultures would of course have been taken, they would not prove that a seizure was the result of infection.

This leaves metabolic causes, including hypoglycaemia, hypomagnesaemia, hyper- and hyponatraemia and an altered tacrolimus level.

Tacrolimus is metabolised by the cytochrome P450 system of enzymes. This gentleman has been started on clarithromycin as an antibiotic, which inhibits this system and is therefore likely to cause an increased blood concentration of tacrolimus. Side effects of high tacrolimus level

include hyperkalaemia, hypomagnesaemia, hyperglycaemia, hypertension, twitching and seizures. Although checking electrolytes may give clues as to the cause of this gentleman's seizure, and should definitely be done, a tacrolimus level is necessary to prove the diagnosis.

It is also worth keeping in mind that in this type of patient, the suspicion of withdrawal seizures may be high. However, one would expect to see other signs and symptoms earlier on in the admission.

Reference: British National Formulary

## **Tacrolimus**

Tacrolimus is a macrolide used as an immunosuppressant to prevent transplant rejection. It has a very similar action to ciclosporin:

Action of ciclosporin

- decreases clonal proliferation of T cells by reducing IL-2 release
- binds to cyclophilin forming a complex which inhibits calcineurin, a phosphatase that activates various transcription factors in T cells

The action of tacrolimus differs in that it binds to a protein called FKBP rather than cyclophilin

Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less. However, nephrotoxicity and impaired glucose tolerance is more common

### **Question 6 of 69**

A 19 year old girl is brought to the Emergency Department by a friend. She is a first year university student and her friends are concerned her behaviour has altered in the past few weeks. On assessment she is confused with an AMTS of 6/10. She has a flat affect. Cardiorespiratory examination is normal although the respiratory rate is 22 at rest. Oxygen saturations are 97% on air. Heart rate is 85bpm regular and blood pressure is 100/55 mmHg.

Examination of her neurological system reveals prominent paraesthesia in both feet with absent vibration sense and proprioception. The ankle and knee reflexes are absent and plantar responses are extensor. There is mild distal weakness in the legs with MRC grading 4/5. Examination of the cranial nerves shows no evidence of nystagmus but visual acuity is reduced to 6/20

bilaterally. She has an ataxic gait.

Her medical history is significant only for coeliac disease and she is taking no regular medications.

Routine blood results show:

Haemoglobin	7.6g/L	Sodium	137mmol/L	Magnesium	0.81mmol/L
Cell volume	103.2fL	Potassium	4.6mmol/L	CRP	4.5mg/L
White cells	5.9x10 <sup>9</sup> /L	Urea	1.9mmol/L	Thyroid tests	Normal
Neutrophils	4.0x10 <sup>9</sup> /L	Creatinine	55mol/L	HIV	Negative
Lymphocytes	1.9x10 <sup>9</sup> /L	Calcium (corr)	2.43mmol/L	Syphilis	Negative
Platelets	300x10 <sup>9</sup> /L	Phosphate	1.01mmol/L		

The patient's friend tells you she has recently started using recreational party drugs.

Which of the following inhaled recreational drugs most explains the above picture?

[Crack \(cocaine\) 7% H \(heroin\) 6% Hippie crack \(nitrous oxide\) 33% Poppers \(amyl nitrate\) 31% Spice \(synthetic cannabinoid\) 23%](#)

Nitrous oxide use can precipitate severe vitamin B12 deficiency with pronounced neurological and haematological signs, particularly in susceptible individuals

The above vignette describes a state of profound vitamin B12 deficiency with clinical signs of subacute combined degeneration of the cord. The constellation of signs of ataxia, loss of deep tendon reflexes with dorsal column signs (loss of proprioception and vibration sense) and paraesthesias with positive Babinski response are known as myelosis funicularis and is highly suggestive of B12 deficiency. In this patient there are also signs of confusion and of reduced visual acuity which increase likelihood of B12 deficiency.

Nitrous oxide, also known as nitrous, hippie crack, laughing gas or whippet, is a relatively recent addition to the arsenal of recreational drugs of abuse. It is sold as cartridges to the catering industry for use in making whipped cream, but can be released and inhaled directly or through balloons or bags. Erroneously regarded as a safe drug it is reported to cause euphoric symptoms in users with a brief onset of actions. It is used clinically as a dental anaesthetic and anxiolytic and hence also promotes feelings of relaxation, detachment and sensory changes. Deaths have been reported due to hypoxia since catering nitrous oxide is not mixed with oxygen as it is when used medically.

Nitrous oxide can cause a rapid depletion in vitamin B12 stores in users, particularly in susceptible individuals such as vegans, anorexics, coeliac patients and those with problems with intestinal absorption. Nitrous oxide reacts with cobalt in the vitamin B12 molecule converting it from an active to an inactive bivalent form, thereby rendering it unusable in vivo. Symptoms of rapid neurological and haematological deterioration can occur including subacute combined degeneration of the cord, depression, dementia, psychosis and blindness, as well as megaloblastic

anaemia. Chronic use can lead to pancytopenia. In the acute phase, symptoms are reversible on cessation of the drug and high dose vitamin B12 supplementation. Chronic users may suffer irreversible neurological damage.

Poppers (amyl nitrate) cause euphoria and sensory dissociation on inhalation but long term effects are rare. A serious complication of their use is the oxidation of ferrous ions within haemoglobin molecules to ferric ions, creating methaemoglobinaemia, reducing the oxygen delivering capacity of the blood. They are not indicated in vitamin deficiencies.

Crack cocaine causes myriad sympathomimetic and serotonergic effects in users but is not directly attributable to anaemia or avitaminosis although this can occur secondarily in the serotonin syndrome. Crack cocaine can also cause choreoathetoid movements in some users. Similarly, heroin causes analgesic and depressant effects at opioid receptors but is not attributable directly to haematological or neurological symptoms although these may be seen in long term users due to self neglect. Spice is a synthetic cannabinoid drug with similar but augmented effects to cannabis. CNS effects of its use include agitation, confusion, psychosis, convulsions, nystagmus and blindness. It is rare for haematological effects to occur although renal failure may be seen.

## **Novel psychoactive substances**

Novel psychoactive substances is the medical term for the many new substances which are chemically related to established recreational drugs such as MDMA and cannabis. They are often referred to as 'legal highs' although this is a misnomer in the UK, as their distribution and sale have been illegal since 2016.

The information below describes some of the common types:

### **Stimulants**

- similar to MDMA, amphetamines and cocaine, resulting in increased levels of serotonin, dopamine and noradrenaline, resulting in a 'high' and feeling of euphoria
- a common example is a stimulant NPS is mephedrone ('bath salts', 'M-CAT', 'meow meow'). It is a cathinone and structurally similar to khat, a plant found in East Africa
- another example is benzylpiperazine ('Exodus', 'Legal X', 'Legal E')
- typically swallowed as a pill/powder ('bombing') or snorted
- adverse effect profile similar to MDMA/cocaine, with the risk of serotonin syndrome

### **Cannabinoids**

- termed synthetic cannabinoid receptor agonists
- commonly referred to as 'spice'
- typically sprayed on to herbal mixtures which are then smoked. Also available in liquid form which is then inhaled using e-cigarettes
- similar adverse effects to cannabis

## Hallucinogenics

- can be either dissociatives and psychedelics
- dissociatives produce a similar effect to ketamine, with a sense of not being connected to the physical body or time. A common dissociative NPS is methoxetamine ('mexxy')
- psychedelics have a similar effect to LSD although NPS versions may also be a stimulant

## Depressant

- can be either opioid or benzodiazepine-based
- usually taken as a pill or a powder
- often structurally very similar to the original drug class, hence the adverse effects are similar
- benzodiazepine NPS often have a significantly longer half-life

## Other substances include:

- Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL): 'G', 'Geebs' or 'Liquid Ecstasy'
- Nitrous oxide: 'Hippie crack'

For a more detailed overview please see the excellent review in BMJ 2017;356:i6848

## Question 7 of 69

A 35-year-old farmer who is in financial difficulties presents to the Emergency department some 40 minutes after taking an unknown amount of paraquat-based weed killer. On arrival in the Emergency department, he has a Glasgow coma scale score of 15 and tells you he regrets what he has done. He feels sick and says there is a burning sensation in his mouth. On examination his blood pressure is 135/80 mmHg, his pulse is 85 beats per minute and regular. There are no abnormal physical signs. Which of the following is the most important intervention?

[Administration of emetic6% Gastric lavage32% IV normal saline8% IV sodium bicarbonate11% Oral fuller's earth43%](#)

Both activated charcoal and fuller's earth are recognised to adsorb paraquat in vitro. They are thought to be most effective when given in the first two hours after overdose, although benefit may still be present up to 12hrs after ingestion. Neither has significant toxicity issues.

Gastric lavage is not recommended. Administration of emetic risks spreading caustic material further, potentially driving greater absorption of paraquat. IV normal saline and IV sodium bicarbonate do not affect prognosis in paraquat overdose. No anti-inflammatory, immunosuppressive, or anti-oxidant interventions have demonstrated a benefit either.

## Overdose and poisoning: management

The table below outlines the main management for common overdoses:

<b>Toxin</b>	<b>Treatment</b>
	Management
<b>Paracetamol</b>	<ul style="list-style-type: none"> <li>activated charcoal if ingested &lt; 1 hour ago</li> <li>N-acetylcysteine (NAC)</li> <li>liver transplantation</li> </ul>
	Management
<b>Salicylate</b>	<ul style="list-style-type: none"> <li>urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning</li> <li>haemodialysis</li> </ul>
<b>Opioid/opiates</b>	Naloxone
<b>Benzodiazepines</b>	Flumazenil
	Management
<b>Tricyclic antidepressants</b>	<ul style="list-style-type: none"> <li>IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity</li> <li>arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias</li> </ul>

<b>Toxin</b>	<b>Treatment</b>
	<ul style="list-style-type: none"> <li>dialysis is ineffective in removing tricyclics</li> </ul>
	Management
<b>Lithium</b>	<ul style="list-style-type: none"> <li>mild-moderate toxicity may respond to volume resuscitation with normal saline</li> <li>haemodialysis may be needed in severe toxicity</li> <li>sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion</li> </ul>
<b>Warfarin</b>	Vitamin K, prothrombin complex
<b>Heparin</b>	Protamine sulphate
	Management
<b>Beta-blockers</b>	<ul style="list-style-type: none"> <li>if bradycardic then atropine</li> <li>in resistant cases glucagon may be used</li> </ul>
	Management has changed in recent times
<b>Ethylene glycol</b>	<ul style="list-style-type: none"> <li>ethanol has been used for many years</li> <li>works by competing with ethylene glycol for the enzyme alcohol dehydrogenase</li> <li>this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning</li> <li><b>fomepizole</b>, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol</li> <li>haemodialysis also has a role in refractory cases</li> </ul>
	Management
<b>Methanol poisoning</b>	<ul style="list-style-type: none"> <li>fomepizole or ethanol</li> <li>haemodialysis</li> </ul>
	Management
<b>Organophosphate insecticides</b>	<ul style="list-style-type: none"> <li>atropine</li> <li>the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit</li> </ul>
<b>Digoxin</b>	Digoxin-specific antibody fragments
<b>Iron</b>	Desferrioxamine, a chelating agent



Toxin	Treatment
<b>Lead</b>	Dimercaprol, calcium edetate Management
<b>Carbon monoxide</b>	<ul style="list-style-type: none"> <li>• 100% oxygen</li> <li>• hyperbaric oxygen</li> </ul>
<b>Cyanide</b>	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate

#### Question 8 of 69

A 17-year-old girl is brought to the Emergency Department by ambulance after her drink was 'spiked' at a party. Her friends recall her complaining that she felt like she was having an 'out of body experience' and that everything she touched seemed artificial. Over the next hour, she became increasingly distressed, slurring her words and appearing off-balance when walking.

Her past medical history is unremarkable. Her friends state that she does not usually partake in recreational drug use and had only consumed 2 or 3 alcoholic drinks during the course of the evening.

Examination reveals a slim young female with a temperature of 37.3, a pulse of 113bpm and a blood pressure of 137/76mmHg. Her pupils measure 5mm in diameter and she is GCS 14/15 due to persistent confusion. Her chest is clear and her heart sounds are unremarkable. Her abdomen is soft and non-tender. Neurological examination reveals bi-directional nystagmus and truncal ataxia with no focal weakness. Her deep tendon reflexes are brisk and symmetrical.

Which drug is she most likely to have been exposed to?

[Ecstasy19% Methoxetamine25% Cocaine7% Gamma-hydroxybutyric acid \(GHB\)29% Nexus \(2C-B\)20%](#)

Both ecstasy and cocaine could cause the tachycardia, hypertension, mydriasis and marginally elevated temperature described in the above scenario. The 'dead giveaway' however, is the presence of dissociative symptoms in combination with an acute cerebellar syndrome, pointing strongly towards methoxetamine intoxication.

Methoxetamine is an analogue of ketamine; a dissociative anaesthetic that acts as a NMDA receptor antagonist. Its effects are typical of the adverse effects of ketamine and include tachycardia, hypertension, mydriasis, confusion and agitation. Nystagmus, dysarthria, and ataxia can be severe and persist for several days.

GHB is a relatively short-acting CNS depressant that causes euphoria followed by coma. Patients can often be roused by external stimuli before returning to a comatose state. Rapid, spontaneous recovery can occur and patients have been known to extubate themselves.

Nexus (2C-B) is a synthetic phenylethylamine with psychoactive and stimulant effects. It is typically snorted or ingested with the former typically causing intense nasal pain. Its effects on the CNS include euphoria, synaesthesia, hallucinations and increased visual and tactile sensation, and probably occur due to antagonism of the 5HT<sub>2</sub> receptor. Nexus (2C-B) is also an alpha-1 receptor agonist and its use can lead to ischaemic complications.

## **Novel psychoactive substances**

Novel psychoactive substances is the medical term for the many new substances which are chemically related to established recreational drugs such as MDMA and cannabis. They are often referred to as 'legal highs' although this is a misnomer in the UK, as their distribution and sale have been illegal since 2016.

The information below describes some of the common types:

### **Stimulants**

- similar to MDMA, amphetamines and cocaine, resulting in increased levels of serotonin, dopamine and noradrenaline, resulting in a 'high' and feeling of euphoria
- a common example is a stimulant NPS is mephedrone ('bath salts', 'M-CAT', 'meow meow'). It is a cathinone and structurally similar to khat, a plant found in East Africa
- another example is benzylpiperazine ('Exodus', 'Legal X', 'Legal E')
- typically swallowed as a pill/powder ('bombing') or snorted
- adverse effect profile similar to MDMA/cocaine, with the risk of serotonin syndrome

### **Cannabinoids**

- termed synthetic cannabinoid receptor agonists
- commonly referred to as 'spice'
- typically sprayed on to herbal mixtures which are then smoked. Also available in liquid form which is then inhaled using e-cigarettes
- similar adverse effects to cannabis

### **Hallucinogenics**

- can be either dissociatives and psychedelics
- dissociatives produce a similar effect to ketamine, with a sense of not being connected to the physical body or time. A common dissociative NPS is methoxetamine ('mexxy')
- psychedelics have a similar effect to LSD although NPS versions may also be a stimulant

## Depressant

- can be either opioid or benzodiazepine-based
- usually taken as a pill or a powder
- often structurally very similar to the original drug class, hence the adverse effects are similar
- benzodiazepine NPS often have a significantly longer half-life

## Other substances include:

- Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL): 'G', 'Geebs' or 'Liquid Ecstasy'
- Nitrous oxide: 'Hippie crack'

For a more detailed overview please see the excellent review in BMJ 2017;356:i6848

## Question 9 of 69

A 67 year old man is admitted to the Emergency Department following a deliberate overdose of an unknown drug. On assessment he is unwell and vomiting although he is maintaining an airway. Oxygen saturations are 100% on 15L/min supplemental oxygen and his respiratory rate is 32/min. His chest is clear and heart sounds are rapid. An ECG shows sinus tachycardia with a rate of 135bpm, a broad QRS complex and a QTc 520msec. His skin is flushed and hot. He complains of ringing in his ears and visual blurring as well as abdominal pain. Tympanic temperature is 37.5°C.

## Blood results show:

Haemoglobin	101g/L	Sodium	131mmol/L	pH	7.11
White cells	7.8x10 <sup>9</sup> /L	Potassium	2.9mmol/L	pCO2	2.4kPa
Platelets	97x10 <sup>9</sup> /L	Urea	9.3mmol/L	pO2	78.4kPa
INR	1.3	Creatinine	198µmol/L	HCO3-	6.3mmol/L
APTT	33secs	Glucose	2.8mmol	BE	-19.7
		Chloride	94mmol/L	Lactate	2.4mmol/L

During assessment he has a generalised tonic-clonic seizure.

Which of the following drugs is he most likely to have overdosed on?

[Ibuprofen9% Isocarboxazid7% Paracetamol3% Quinine56% Venlafaxine25%](#)

Quinine toxicity (cinchonism) presents with myriad ECG changes, hypotension, metabolic acidosis, hypoglycaemia and classically tinnitus, flushing and visual disturbances. Flash pulmonary oedema may occur

Paracetamol toxicity presents with early hepatotoxicity and coagulopathy, and later renal failure and encephalopathy which are features lacking in this clinical scenario.

Ibuprofen, a non-steroidal anti-inflammatory, is relatively safe in overdose although massive ingestion may cause gastrointestinal ulceration and haemorrhage as well as electrolyte imbalances, coagulopathy and prominent cerebellar signs. This is not commented upon in the clinical vignette.

Venlafaxine is a selective serotonin and noradrenaline reuptake inhibitor and presents with symptoms of serotonin and sympathetic overdrive in poisoning, including agitation, sweating, hyperpyrexia, clonus, tachycardia and hypertension. ECG abnormalities similar to the above may occur, as may hypoglycaemia but venlafaxine is not the most likely agent.

Isocarboxazid is a monoamine oxidase inhibitor and in overdose may also cause symptoms of the serotonin syndrome although sympathomimetic features tend to predominate, including hyperglycaemia.

### **Quinine toxicity (cinchonism)**

Quinine is a remarkably toxic drug; something which is not so readily acknowledged. It is used as an antimalarial drug and also as a prophylactic agent against leg cramps, although both uses are increasingly falling from vogue due to the availability of better, safer agents. Quinine toxicity, known as cinchonism, may be fatal, usually by cardiac arrhythmia or flash pulmonary oedema in the short term, although incipient renal failure may be fatal more long-term.

Cardiac arrhythmia is a common finding in cinchonism due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively and these rhythms may degenerate into ventricular tachyarrhythmias or fibrillation causing death. Hypoglycaemia is also a common finding in cinchonism since quinine stimulates pancreatic insulin secretion and this should be corrected rapidly if present. Unlike in the above case, flash pulmonary oedema may develop

causing hypoxia and necessitating positive pressure ventilation. Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed and dry skin and abdominal pain.

Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen. In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods. Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.

Management of quinine poisoning is largely supportive with fluids, inotropes and bicarbonate as needed as well as positive pressure ventilation for pulmonary oedema.

#### Question 10 of 69

The patient below has noticed a gradual change to his facial skin since starting a new medication a few months ago:



© Image used on license from [DermNet NZ](#)

Which drug has he been taking?

[Amiodarone 60%](#) [Phenytoin 16%](#) [Ciclosporin 10%](#) [Digoxin 5%](#) [Sildenafil 9%](#)

Patients taking amiodarone may develop a 'slate-grey' appearance.

## Amiodarone: adverse effects

Amiodarone is associated with a wide variety of adverse effects.

- thyroid dysfunction: both hypothyroidism and hyperthyroidism
- corneal deposits: present in most patients, rarely interfere with vision, usually reversible on withdrawal of drug
- pulmonary fibrosis/pneumonitis
- liver cirrhosis/hepatitis
- peripheral neuropathy, myopathy
- photosensitivity
- 'slate-grey' appearance
- prolonged QT interval
- thrombophlebitis and injection site reactions
- bradycardia

Important drug interactions of amiodarone include:

- decreased metabolism of warfarin, therefore increased INR
- increased digoxin levels

### Question 1 of 59

A 19-year-old male is found collapsed in a dark alley. He is of no known abode. He is very drowsy but oriented to person, place and time with a Glasgow coma scale of 14/15 (E3, V5, M6). He smells of alcohol but denies having consumed any. His clinical examination is significant for impairment in visual acuity bilaterally. He has a tremor of his outstretched hands but the rest of his examination is normal. His blood pressure is 145/76mmHg with a pulse of 101/min regular, respiratory rate of 22/min and an oxygen saturation of 95% on room air.

Investigations:

Hb	11.3 g/dl
MCV	102 fl
Platelets	$110 \times 10^9/l$
WBC	$12 \times 10^9/l$
Creatinine	117 $\mu\text{mol/L}$
Urea	9 $\mu\text{mol/L}$
Na+	146 mmol/L
K+	5.4 mmol/L

CL- 109 mmol/L

Arterial blood gas:

pH 7.21

PaO<sub>2</sub> 10.9 kPa

PaCO<sub>2</sub> 4.2 kPa

HCO<sub>3</sub> 16 mEq/L

Considering the ingested toxin, what is the next best step in your management?

[Fomepizole 71% N-acetyl cysteine 5% Activated charcoal 5% Gastric lavage 4% Sodium bicarbonate 15%](#)

Answer: Fomepizole or 4-methylpyrazole.

This patient has ingested methanol. Clue to this is the fact that he smells of alcohol but denies having consumed any, though definitive diagnosis is based on a raised serum methanol level. Initial symptoms are similar to those felt in alcohol intoxication including ataxia, disinhibition, headaches, nausea and vomiting. These are followed by drowsiness which may progress to coma. Metabolic acidosis with raised anion gap is common.

He has visual impairment indicating severe methanol toxicity. Visual signs present in methanol toxicity include, photophobia, blurred vision, poor visual acuity and blindness. Fundoscopy could reveal optic disc swelling or pseudoglaucomatous changes.

This patient needs urgent treatment with i.v fomepizole. If this is not available then i.v ethanol is an adequate alternative though it will produce symptoms similar to alcohol intoxication.

Fomepizole acts by inhibiting the primary step in the conversion of methanol to formic acid, a highly toxic metabolite. Specifically it competitively inhibits alcohol dehydrogenase, the enzyme that converts methanol to formaldehyde which is then further oxidised to formic acid by formaldehyde dehydrogenase.

The signs of methanol toxicity are caused by formic acid so inhibition of its synthesis is a very important step in its management.

Dialysis may be needed to help rapid elimination of the toxin from the system. The following are the indications for haemodialysis in methanol intoxication:

- worsening acidosis despite sodium bicarbonate treatment
- visual involvement
- quantity of consumed methanol exceeding 30ml
- serum methanol level greater than 20mg/dl

Other conditions that may be present in methanol toxicity include:

- seizures
- cardiac arrhythmias and heart failure
- haemorrhagic pancreatitis
- parkinsonism secondary to haemorrhagic and non haemorrhagic damage to the basal ganglia

He is acidotic and whilst sodium bicarbonate could help with acidosis it is unlikely to lead to overall improvement.

N-acetyl cysteine is used in paracetamol overdose.

Further reading:

Acute bilateral blindness caused by accidental methanol intoxication during fire 'eating'

C Cursiefen, A Bergua <http://bj.o.bmj.com/content/86/9/1064.full>

## **Methanol poisoning**

Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc) and also specific visual problems, including blindness. These effects are thought to be secondary to the accumulation of formic acid. The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of optic neuropathy

Management

- fomepizole or ethanol
- haemodialysis

### **Question 2 of 59**

A 47-year-old Latvian man is brought to the Emergency Department by two of his friends. He is confused and aggressive and walks with an unsteady gait. History is difficult to obtain from the patient due to slurring of his speech and a slight language barrier. You note that he fails to meet your gaze when you are talking to him. Examination shows a GCS of 15/15 but he is drowsy and



irritable. There is a vague smell of alcohol on his breath. He is flushed in the face and his eyes are red and hyperaemic. Pupils are slow to react to direct light but equal in size. The cardiorespiratory examination is unremarkable aside from a respiratory rate of only 8/min but SpO<sub>2</sub> is 98% on air. The abdomen is soft and non-tender with no hepatomegaly and no signs of chronic liver disease. Despite the department being well lit, he asks you to turn the lights on.

Biochemistry reveals:

Haemoglobin	149g/L	Sodium	150mmol/L	pH	7.25
White cells	8.9x10 <sup>9</sup> /L	Potassium	5.9mmol/L	pCO <sub>2</sub>	3.9kPa
Neutrophils	5.9x10 <sup>9</sup> /L	Urea	13.8mmol/L	pO <sub>2</sub>	12.6kPa (air)
Platelets	229x10 <sup>9</sup> /L	Creatinine	156mol/L	HCO <sub>3</sub> <sup>-</sup>	12.5mmol/L
Prothrombin time	11 sec	Glucose	24.7mmol/L	BE	-13.2mEq/L
Ethanol	110mg/dL	Chloride	100mmol/L	Lactate	2.0mmol/L
Anion gap	38	Osmolar gap	25 (-10 to +15)		

What is the most appropriate next step in the management of this patient?

[Begin high dose oral folic acid and vitamin B complex 5%](#)  
[Establish IV access and begin fast fluids with Pabrinex I+II \(Vitamin B12\) 10%](#)  
[Establish IV access and send blood for methanol levels; give oral ethanol in the form of neat 40% whisky at a dose of 175ml 12%](#)  
[Establish IV access and send blood for methanol levels; begin IV fomepizole 1000mg in 500ml 5% dextrose over 30 minutes 62%](#)  
[Refer to Intensive Care to begin haemofiltration 11%](#)

Methanol poisoning is preferentially treated with IV fomepizole; this should be commenced immediately the suspicion is raised

The clinical picture in this scenario is typical of an acute alcohol intoxication syndrome with descriptors of ataxia, confusion, aggression and drowsiness. Often there will be a smell of alcohol present when examining the patient and unfortunately, a coherent history is often absent due to poor compliance and often incapacity. However, in the vignette, there are features which might not be expected with a case of ethanol intoxication such as difficulties with vision, often detected by the failure of making any eye contact or of requesting extra lighting in a well-lit room. This suggests damage to the optic nerve and is a feature of methanol poisoning. Methanol toxicity is often very difficult to distinguish from ethanol intoxication but visual symptoms should prompt consideration coupled with a careful history.

Similar to drinkable ethanol, methanol is rapidly metabolised by hepatic enzymes; ethanol dehydrogenase converts methanol to formaldehyde and aldehyde dehydrogenase further metabolises this to formic acid (formate) which is extremely toxic to the central nervous system. Accumulation of formate in the central nervous system leads not only to cellular hypoxia due to interruption of mitochondrial cytochrome activity but also a profound acidosis. Coupled with this methanol itself, similar to ethanol, causes central nervous and respiratory depression further augmenting its toxicity.

Typically bloods will show a metabolic acidosis with a high anion gap - often co-ingestion of

ethanol will have occurred and this may account for some of the unmeasured ions but often the plasma ethanol level will not be sufficiently raised to explain it in totality. Calculation of the osmolar gap may also be elevated initially which is not seen so much with ethanol toxicity.

Treatment of methanol toxicity is by blockade of the metabolism of methanol to formate leading to renal clearance of the unmetabolised methanol. Both ethanol and fomepizole are competitive inhibitors of methanol metabolism as they preferentially have an affinity for both ethanol dehydrogenase and aldehyde dehydrogenase and so toxic formate is not produced. Fomepizole, although very expensive, is preferentially used over ethanol as there is a risk of precipitating ethanol toxicity with its associated central nervous and respiratory depression. If ethanol is used as an antidote, regular monitoring of plasma ethanol concentrations are needed to ensure maintenance within the range of 100-200mg/dL. In this case, plasma ethanol levels are within this range anyway and methanol toxicity is still occurring. Both fomepizole and ethanol need to be continued until plasma methanol concentrations fall below <50mg/L.

In addition, intravenous folinic acid should be given as this aids in the speedy metabolism of formic acid and helps in reducing the central nervous toxicity. Unfortunately, oral folic acid is insufficiently rapidly absorbed to be helpful in this situation. Supplementation of B vitamins is important in cases of any alcohol toxicity as this avoids development of Wernicke's encephalopathy and this should take the form of Pabrinex I+II, however, it is not the most pressing concern in a potential methanol toxicity case. Oral vitamin B complex is important in chronic alcoholism but not in an acute situation. Haemofiltration is a potential mechanism for clearing methanol from the circulation, however, this is usually reserved for occasions when fomepizole fails or is not tolerated.

In cases of methanol toxicity, an intensive care opinion may be useful however as central venous access may be required to administer bicarbonate in severe acidosis or in case of respiratory depression requiring intubation and assisted ventilation.

Note that in cases of suspected methanol poisoning, commencing an antidote immediately is important and should be done before methanol levels have been confirmed.

## **Methanol poisoning**

Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc) and also specific visual problems, including blindness. These effects are thought to be secondary to the accumulation of formic acid. The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of optic neuropathy

### **Management**

- fomepizole or ethanol

- haemodialysis

#### Question 3 of 59

A 23-year-old woman is reviewed following admission for paracetamol overdose. She ingested 25 grams of paracetamol and was started on N-acetylcysteine as her paracetamol level was 812 micromol/L eight hours following ingestion. She feels well, denying any abdominal pain or other symptoms. At what point should N-acetylcysteine be stopped?

[When INR <1.3 and ALT less than 2x upper limit34%](#) [When abdominal pain resolved4%](#) [When pH is >7.3518%](#) [When paracetamol levels become undetectable17%](#) [After 48 hours27%](#)

The correct answer is when INR <1.3 and ALT less than 2x upper limit. Note that the primary measure of synthetic liver function is clotting which is why it is so closely monitored in paracetamol overdose and helps indicate when the liver is improving. pH is a useful measure for criteria for a liver transplant but is not helpful in most cases as it generally remains normal despite severe liver dysfunction. Abdominal pain is often present but not always and is therefore not a very sensitive marker. Paracetamol levels do not reflect the extent of liver damage and they can be very difficult to interpret in staggered overdoses. Depending on the extent of liver damage, treatment may need to be longer than 48hrs and in some cases shorter.

### Paracetamol overdose: management

#### Management

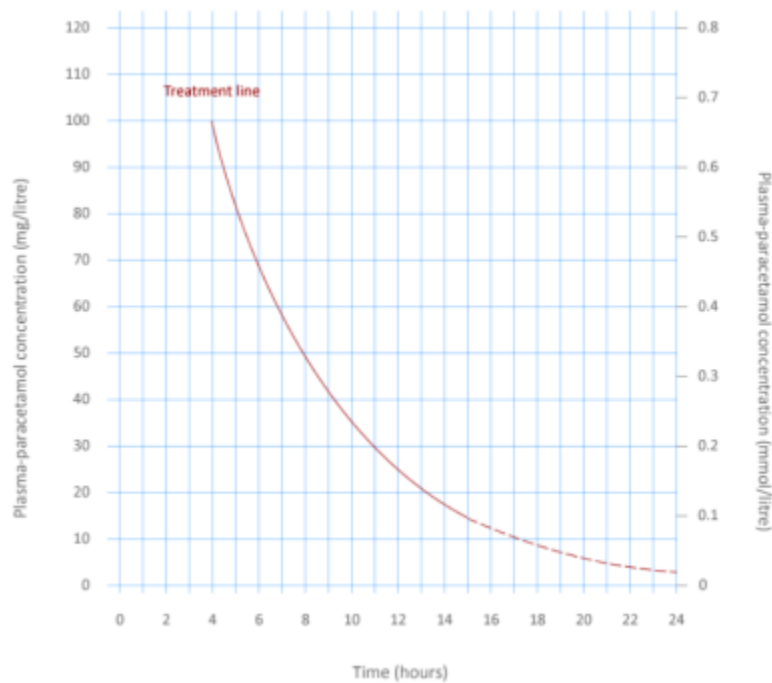
The following is based on 2012 Commission on Human Medicines (CHM) review of paracetamol overdose management. The big change in these guidelines was the removal of the 'high-risk' treatment line on the normogram. All patients are therefore treated the same regardless of risk factors for hepatotoxicity. The National Poisons Information Service/TOXBASE should always be consulted for situations outside of the normal parameters.

Acetylcysteine should be given if:

- there is a staggered overdose\* or there is doubt over the time of paracetamol ingestion, regardless of the plasma paracetamol concentration; or

- the plasma paracetamol concentration is on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours, regardless of risk factors of hepatotoxicity

Acetylcysteine is now infused over 1 hour (rather than the previous 15 minutes) to reduce the number of adverse effects.



### King's College Hospital criteria for liver transplantation (paracetamol liver failure)

**Arterial pH < 7.3, 24 hours after ingestion**

**or all of the following:**

- prothrombin time > 100 seconds**
  - creatinine > 300  $\mu$ mol/l**
- grade III or IV encephalopathy**

\*an overdose is considered staggered if all the tablets were not taken within 1 hour

#### Question 4 of 59

A 45-year-old man was found unconscious at home by his partner, with empty packs of flecainide, codeine and valerian root tablets besides him. He was only found after his partner got worried when he had locked himself in his room and after 4 hours not heard any sounds from the room. He had been depressed for the past couple of months and relations between him and his partner had been strained. He has a past medical history of back pain, paroxysmal atrial fibrillation, angina and hypertension.

On examination, he was drowsy, unable to give a history, with a heart rate of 50bpm, respiratory rate of 16 breaths per minute, oxygen saturation of 96% on air, and a blood pressure of 110/58mmHg. Pupils were 3mm and equal and reactive to light.

#### Investigations:

Na+	136 mmol/l
K+	4.6 mmol/l
Urea	10.9 mmol/l
Creatinine	110 µmol/l
Serum bilirubin	30 µmol/l
Serum alkaline phosphatase	135 IU/l
Serum aspartate aminotransferase	50 IU/l
C Reactive protein	2mg/l
Haemoglobin	14.6 g/dl
White cell count	5.6 x 10 <sup>9</sup> /L
INR	1.4

#### ABG (on air):

pH	7.258
pO <sub>2</sub>	11.7 kPa
pCO <sub>2</sub>	3.4 kPa
Lactate	1.6 mmol/l
Base Excess	-8.4 mmol/l
Bicarbonate	11.9 mmol/l

ECG showed bradycardia with widened QRS complexes and giant inverted T waves.

After fluid resuscitation, what is the next single most important management step?

[Activated Charcoal](#)7%[Magnesium Sulphate](#)21%[Sodium Bicarbonate](#)56%[Haemodialysis](#)11%[N-Acetyl Cysteine infusion \(NAC\)](#)6%

This patient has overdosed on a number of medications, the most toxic being codeine and flecainide. He has evidence of cardiac arrhythmias, bradycardia and metabolic acidosis consistent with flecainide overdose, and also mildly deranged liver functions. There is no evidence of respiratory depression.

Flecainide is a class 1c antiarrhythmic, which blocks sodium channels leaving the action potential unchanged. Cardiac features predominate, causing bradycardia, hypotension, nodal and ventricular tachycardia. ECG abnormalities include marked prolongation of the QRS and Q-T interval and giant inverted T waves. Other features include hypoxia, respiratory depression, metabolic acidosis, and reduced renal function. Nausea, vomiting, coma and convulsions have been reported.

As the time of ingestion is unknown, possibly up to 4 hours ago, he has probably missed the window for gastric decontamination with activated charcoal. The presence of QRS prolongation and acidosis would require rapid correction with sodium bicarbonate infusions, ideally via a central line, to reverse the effects of flecainide.

Haemodialysis are of no value in eliminating flecainide from the system. Magnesium is indicated if there is evidence of a prolonged QT interval. NAC is indicated for paracetamol overdose.

Valerian root tablets are herbal sleeping remedies and do not have lasting side effects if taken in large quantities.

## **Flecainide**

Flecainide is a Vaughan Williams class 1c antiarrhythmic. It slows conduction of the action potential by acting as a potent sodium channel blocker. This may be reflected by widening of the QRS complex and prolongation of the PR interval

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction. The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to increase mortality post myocardial infarction and is therefore contraindicated in this situation

### **Indications**

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

## Adverse effects

- negatively inotropic
- bradycardia
- proarrhythmic
- oral paraesthesia
- visual disturbances

## Question 5 of 59

A 29 year old man is brought to the Emergency Department by ambulance after being found collapsed at home by his father. The patient had a known history of major depression and was found next to two empty bottles of fluoxetine which he had been prescribed by his psychiatrist. His father reported that he had found a suicide note at the patients home.

On arrival in hospital the patient was extremely agitated and unable to give a clear history. Initial assessment was as documented below.

## Airway

- Patient's own

## Breathing

- Respiratory rate 28
- Some increased work of breathing
- O2 saturation 100 % (10 L via non-rebreath mask)
- Air entry throughout chest with vesicular breath sounds

## Circulation

- BP 190 / 100 mmHg
- HR 120 bpm, pulse regular
- JVP not elevated
- Heart sounds normal

## Disability

- Temperature 38.4°C
- Flushed and sweaty
- Patient agitated and distressed
- Pupils equal and reactive
- Rapid, involuntary horizontal and vertical conjugate fast eye movements
- Good power in all arms and legs 10 beats of clonus on ankle dorsiflexion, mild increase in general muscle tone Reflexes very brisk and symmetrical in arms and legs

#### Exposure

- Abdomen soft and non-tender

Results from arterial blood sample (10 L O<sub>2</sub>) were as follows

pH	7.35
PaCO <sub>2</sub>	30 mmHg (reference 32-43)
PaO <sub>2</sub>	159 mmHg (reference 70-100)
Bicarbonate	22.5 mmol / L (reference 20.0-26.0)
Sodium	139 mmol / L
Potassium	4.5 mmol / L
Lactate	2 mmol / L

Electrocardiogram: sinus rhythm at 125 bpm, normal axis, normal QRS, no acute ST / T wave changes

Portable chest x-ray: clear lung fields, no pneumothorax, no rib fractures

Treatment with intravenous fluids and oral diazepam was initiated following primary assessment. A fan was used to help cool the patient. On review 30 minutes later, the patient remained agitated and distressed with persistent clonus and uncontrolled eye movements only slightly improved to previous assessment. Temperature was 38.1 oC

What is appropriate next line treatment for this patient?

[Intravenous chlorpromazine 24% Oral cyproheptadine 42% Intubation and ventilation 17% Further oral diazepam 8% Cooling blanket 9%](#)

The presence of opsidclonus, sustained clonus, agitation, fever and sweating in the context of fluoxetine overdose are consistent with moderate serotonin syndrome. Moderate serotonin syndrome occurs in 15 % of cases of selective serotonin re-uptake inhibitors. Treatment is initially with oral diazepam but if this proves ineffective then oral cyproheptadine is next line therapy with serotonin antagonist and sedating action.



Intravenous chlorpromazine and intubation and ventilation may be required in severe serotonin syndrome associated with severe hyperthermia, coma and rigidity associated with respiratory failure. Additional cooling measures may be indicated in this case but are likely to be insufficient in isolation.

Buckley N, Dawson A, Isbister G. Serotonin syndrome. BMJ 2014;348:g1626.

## **Serotonin syndrome**

### Causes

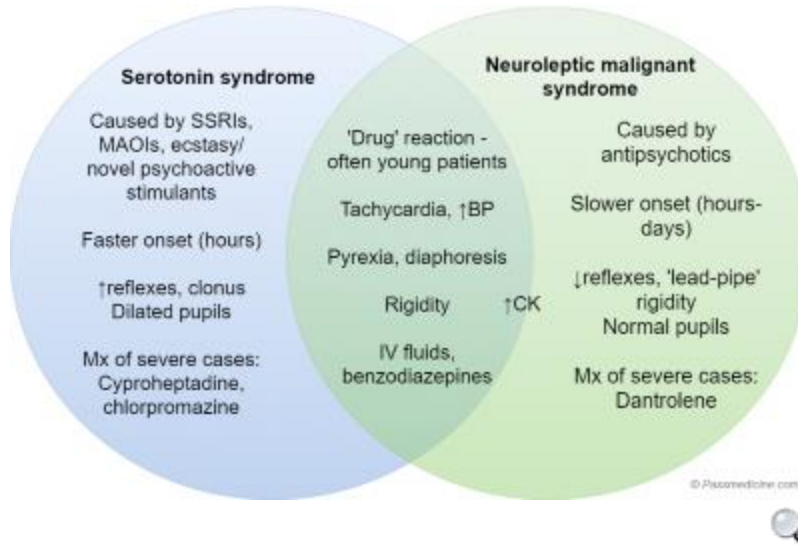
- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines

### Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state

### Management

- supportive including IV fluids
- benzodiazepines
- more severe cases are managed using serotonin antagonists such as cyproheptadine and chlorpromazine



Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

#### Question 6 of 59

A 62-year-old gentleman presents to the emergency department with central chest pain. He describes his pain as a heavy pressure in the middle of his chest which radiates to his left arm. It has improved with the use of his GTN spray, but he did not want to use more than two puffs as he is concerned about getting a headache with its use. He has a past medical history of angina, previous myocardial infarction three years ago and he is a current smoker with a 25 pack-year history.

His ECG demonstrates ST depression in V3 to V5 of 2mm, pathological Q waves and T wave inversion. His troponin is raised at 350ng/L. He is given aspirin, clopidogrel and morphine. His pain settles and he starts to feel comfortable. He has a high GRACE (Global Registry of Acute Coronary Events) score at 122, meaning that he has a 7.9% chance of death within 6 months. Following discussion with the cardiology registrar will be scheduled for an angiogram within 12 hours. How should his acute coronary syndrome be further managed?

[Fondaparinux37%](#) [No further anticoagulants11%](#) [Unfractionated heparin42%](#) [Heparin sodium7%](#) [Warfarin3%](#)

The correct answer is unfractionated heparin. This is a patient who has presented with chest pain and diagnosed with an NSTEMI and deemed to be at sufficiently at high risk to warrant an urgent angiography. NICE recommends that patients should be treated with aspirin and clopidogrel immediately and this should be combined with fondaparinux unless at high risk of bleeding or angiography is planned within 24 hours. If angiography is planned, then

unfractionated heparin should be used. This is because angiography has a risk of haematoma formation and this risk is increased when fondaparinux is used compared to unfractionated heparin as the latter has a much shorter half-life.

Source:

'Unstable angina and NSTEMI: early management' Clinical guideline [CG94]. The National Institute for Health and Care Excellence, March 2010.

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	Standard heparin	Low molecular weight heparin (LMWH)
<b>Administration</b>	Intravenous	Subcutaneous
<b>Duration of action</b>	Short	Long
<b>Mechanism of action</b>	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
<b>Side-effects</b>	Bleeding Heparin-induced thrombocytopenia (HIT) Osteoporosis	Bleeding Lower risk of HIT and osteoporosis with LMWH
<b>Monitoring</b>	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
<b>Notes</b>	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

Heparin-induced thrombocytopenia (HIT)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

#### Question 7 of 59

A 70 year old woman is brought by ambulance to the Emergency Department after being found unresponsive by her husband. He reported that he had been unable to wake the patient from sleep that morning. He said that she had been previously very well without significant physical medical problems. Her only regular medication was moclobemide which she had taken for many years after an episode of severe depression. The patient's husband had recently been prescribed fluoxetine for an anxiety disorder, although the patient had also been taking this medication for a few days as she felt her mood had been low.

Initial assessment in hospital showed the patient to be extremely unwell with hypertension (blood pressure 190/110 mmHg). and tachycardia (heart rate 130 bpm). She was minimally responsive with severe rigidity of skeletal muscles. Temperature was recorded as exceeding 40°C.

An urgent anaesthetic review was requested and the patient was intubated and ventilated prior to transfer to the intensive care unit. A plan was made for treatment with IV chlorpromazine.

What action is necessary prior to IV chlorpromazine treatment?

[Intravenous midazolam infusion14%](#) [Cardiac monitoring31%](#) [Active cooling with ice packs18%](#) [Intravenous fluid loading32%](#) [Haemodialysis4%](#)

The patient has severe serotonin syndrome secondary to the combination of monoamine oxidase inhibitor and selective serotonin reuptake inhibitor. This is a medical emergency and may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and adult respiratory distress syndrome.

Treatment is with IV chlorpromazine acting as a serotonin antagonist. Intravenous fluid loading is essential prior to IV chlorpromazine to prevent hypotension.

Midazolam infusion may be used in moderate serotonin syndrome to reduce muscular hyperactivity. Active cooling is also an important tool but is unlikely to be sufficient in isolation in this case. Haemodialysis may be required later in admission if renal failure occurs but is not required acutely prior to IV chlorpromazine.

Buckley N, Dawson A, Isbister G. Serotonin syndrome. BMJ 2014;348:g1626.

## **Serotonin syndrome**

### Causes

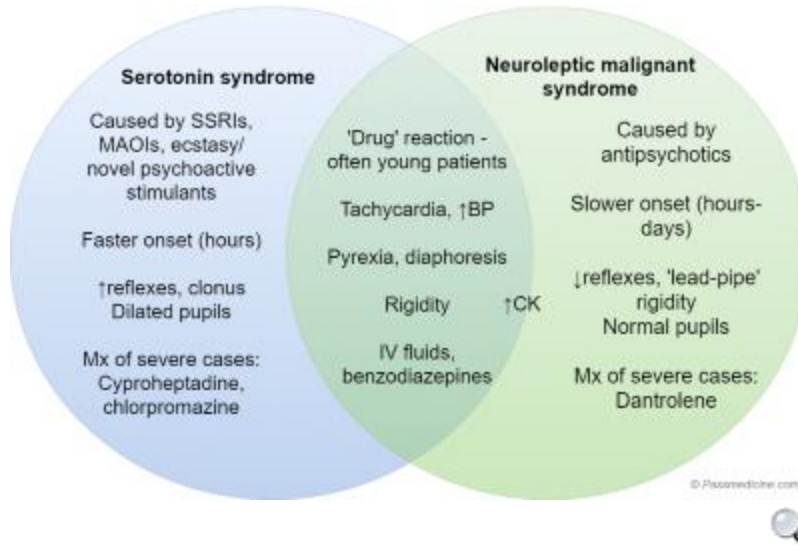
- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines

### Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state

### Management

- supportive including IV fluids
- benzodiazepines
- more severe cases are managed using serotonin antagonists such as cyproheptadine and chlorpromazine



Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

#### Question 8 of 59

A 56 year old gardener is brought to the Emergency Department by his wife. He was bitten on the right hand by a snake while clearing bushes in his back garden. It is identified as a common European adder. There is an obvious, red puncture site on the dorsum of the right hand with significant swelling of the entire hand to the level of the wrist. He is in significant discomfort. Examination reveals a normal cardiovascular examination with a heart rate of 112bpm, blood pressure of 137/90mmHg and normal respiratory rate and oxygen saturations. Capillary glucose is 5.6mmol. ECG shows normal sinus rhythm with normal PR, QRS and QT intervals. Routine blood tests including liver function, electrolytes, creatine kinase, full blood count and arterial blood gases are normal.

Which of the following interventions is the most appropriate at this stage?

[Application of a tourniquet above the site of envenomation to prevent systemic toxicity](#)11% [Bathe the site of envenomation in hot, sterile water to inactivate the venom](#)11% [Intravenous access and rapidly infuse 0.9% sodium chloride with 1g intravenous paracetamol](#)23% [Intravenous access and administer 200mg IV hydrocortisone, 10mg IV chlorphenamine and 0.5mg IM adrenaline 1:1000](#)10% [Intravenous access and administer 10ml adder antivenin in 500ml 0.9% sodium chloride over 30 minutes](#)44%

Adder bites are rare, but when they occur may be extremely painful; the mainstay of treatment is analgesia and supportive therapy. Discuss the use of antivenin with NPIS and do not apply a tourniquet

Application of a tourniquet is absolutely contraindicated since it increases the likelihood of localised necrosis of the affected limb as well as the risk of venous thrombosis which in turn increases the likelihood of central venous thrombosis on release of the tourniquet, as well as cardiac arrhythmia due to the systemic flooding of released potassium and other necrosis factors from tissue damage and haemolysis in a ligatured extremity when the tourniquet is removed.

Unlike venom of the United Kingdom's only other native poisonous animal, the weeverfish (Trachinidae family), viper venom is not heat labile. Application of cold water to a bite may help to assuage pain, but hot water will not deactivate the venom. Weeverfish stings may be treated by bathing the affected limb (usually a foot) in hot water to denature the active proteins.

Adder antivenin is readily available for use in severe bites and can be obtained by contacting local zoos or the National Poisons Information Service. However, severe anaphylactic reactions to the antivenin are common and may be seen in up to 20% of recipients, particularly in atopic or asthmatic individuals. For this reason, antivenin is reserved only for severe systemic envenomations in patients with resistant hypotension, new ECG changes, significant rise in white cell count, raised CK, metabolic acidosis or swelling involving more than half the affected limb or crossing a joint boundary, e.g. beyond the wrist if bitten on the hand. The patient in the above scenario has none of these symptoms. Similarly, in the absence of any symptoms suggestive of an acute anaphylactoid reaction, treatment with adrenaline and hydrocortisone is unnecessary, although antihistamines may help symptomatically. Often, symptomatic treatment is all that is required with analgesia taking priority. Intravenous analgesia is often faster acting and fluids may be required if swelling is significant or vomiting is profuse.

## **Snake bites in the UK**

The common European adder or viper, *Vipera berus*, is the only poisonous snake in the United Kingdom. Adder bites are relatively rare, even in rural areas, and often victims of snake bites are children. Even when bites occur, actual envenomation may not happen. Fatalities are extremely uncommon and since 1876 there have only been 14 recorded deaths due to adder envenomation. Bites by snakes and venom toxicity may be extremely painful locally however, and systemic symptoms may be present. Typical symptoms which may be expected following an adder envenomation include severe local pain, swelling, erythema, paraesthesia, numbness and blood blistering. In the ensuing hours, tracking erythema and significant swelling, often along the lymphatic system, may be seen, as well as compartment syndrome and tissue necrosis. Systemic symptoms similar to anaphylaxis may be seen with hypotension, collapse, airways swelling and compromise, diarrhoea, vomiting and fever; sometimes these may be delayed symptoms. Significant bruising at the site of skin puncture may occur due to the natural pro-coagulants

within the venom. Other symptoms are due to the composition of the venom including cytokines, histamine and myriad enzymes.

Question 9 of 59

A 71-year-old man with a history of chronic obstructive pulmonary disease (COPD) is investigated for back pain. Over the past 10 years he has had numerous admissions for infective exacerbations of COPD and currently uses long-term oxygen therapy. The pain came on suddenly whilst he was at his local supermarket.

A MRI scan is requested:



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



What is the most likely underlying cause of the back pain?



[Osteomyelitis5%Multiple myeloma5%Pott's disease10%Metastatic lung cancer10%Osteoporosis70%](#)

The MRI shows osteoporotic fractures of the 8th and 10th thoracic vertebrae. This is likely to have been caused by repeated courses of steroids to treat exacerbations of COPD.

## **Osteoporosis: management**

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of  $-2.5$  SD or below). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- alendronate is first-line
- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

## **Treatment criteria for patients not taking alendronate**

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patient's age, their T-score and the number of risk factors they have from the following list:

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've

not included them in the revision notes but they may be found by following the NICE link. The most important thing to remember is:

- the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score  $< -3.5$ )
- the strictest criteria are for denosumab

## **Supplementary notes on treatment**

### Bisphosphonates

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

### Vitamin D and calcium

- poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

### Raloxifene - selective oestrogen receptor modulator (SERM)

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

### Strontium ranelate

- 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care

- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- increased risk of cardiovascular events: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- increased risk of thromboembolic events: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

### Denosumab

- human monoclonal antibody that inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

### Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

### Hormone replacement therapy

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

### Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

### Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients



© Image used on license from [Radiopaedia](#)



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

#### Question 10 of 59

An elderly lady brings her 32-year-old lodger into the emergency department after she witnesses him having two generalised seizures, lasting for around 4 minutes before spontaneously terminating, followed by a loss of consciousness lasting for around 10 minutes before slowly becoming rousable again. He is not known to have a history of epilepsy and does not take any regular medications. He denies any history of illicit drugs, smoking or excessive alcohol intake, corroborated by his landlady, who reports not to have seen him ever drinking in the 4 years he has been living in her loft space. Apart from a mild headache, he claims to have been well recently, continuing to work on his start-up computer software in the loft. She states that he has always 'kept himself to himself' in a cluttered dark loft space without a window, with a simple mattress and a small wardrobe. He didn't even ask for an additional heater during the cold winter as he thought 'the loft gas boiler provides enough warmth'. On examination, he is slightly sleepy

but rousable. His Glasgow Coma Score is E4 V5 M6. Apart from erythematous lips, you note no other remarkable features. Neurological examination of his cranial nerves, upper and lower limbs are unremarkable. There is no ophthalmoscope available. His observations are heart rate 90/min and regular, BP 132/88 mmHg, sats 98% on air.

His blood tests demonstrate:

Hb 159 g/l  
Platelets  $282 \times 10^9/l$   
WBC  $7.9 \times 10^9/l$   
  
Na<sup>+</sup> 143 mmol/l  
K<sup>+</sup> 4.2 mmol/l  
Urea 6.1 mmol/l  
Creatinine 88  $\mu$ mol/l  
CRP 3 mg/l

His arterial blood gas demonstrate:

pH 7.25  
PaO<sub>2</sub> 15.8 kPa  
PaCO<sub>2</sub> 2.9 kPa  
Lactate 4.5 mmol/l  
HbCO 24%

A CT head demonstrates a small area of acute ischaemic change in the right globus pallidus.

Which is the most appropriate next management?

[High flow oxygen 68% Aspirin 300mg 13% Clopidogrel 300mg 5% PO chlordiazepoxide 40mg QDS 8% Start levetiracetam 250mg BD 6%](#)

The young patient presents with new seizures on a background of a mild headache, red lips and a significantly raised COHb. This is a history suggestive of carbon monoxide poisoning. The ischaemic change on CT head, particularly in the globus pallidus with haemorrhagic transformation, a classic neurological consequence of carbon monoxide poisoning. It should be noted that pulse oximetry and PaO<sub>2</sub> are commonly normal in CO poisoning. Carbon monoxide reduces haemoglobin binding capacity and not the amount of O<sub>2</sub> dissolved in blood. A metabolic acidosis is present in the blood gas secondary to lactic acidosis from systemic ischaemia. If fundoscopy could have been performed, a cherry-red spot in the macula is the classic finding.

The initial management of CO poisoning is high flow oxygen, which reduces the half-life of CO binding to haemoglobin from 300 to 90 minutes. It is recommended that patients with severe

acidosis ( $\text{pH} < 7.1$ ),  $\text{COHb} > 25\%$ , continued loss of consciousness and severe end organ failure be transferred to a unit for hyperbaric oxygen therapy.

## **Carbon monoxide poisoning**

Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia. There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK

Questions may hint at badly maintained housing e.g. student houses

Features of carbon monoxide toxicity

- headache: 90% of cases
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

Typical carboxyhaemoglobin levels

- $< 3\%$  non-smokers
- $< 10\%$  smokers
- 10 - 30% symptomatic: headache, vomiting
- $> 30\%$  severe toxicity

Management

- 100% oxygen
- hyperbaric oxygen

Indications for hyperbaric oxygen\*

- loss of consciousness at any point
- neurological signs other than headache
- myocardial ischaemia or arrhythmia

- pregnancy

\*as stated in the 2008 Department of Health publication 'Recognising Carbon Monoxide Poisoning'

#### Question 1 of 49

A 27 year old well-nourished male electroplater is admitted to hospital with abdominal pain and neurological symptoms. He tells you that he has had worsening symptoms for the past three months with severe central abdominal pain, diarrhoea, vomiting and painful burning sensation in both feet. He also describes increasing clumsiness with loss of manual dexterity and tripping over his feet frequently. He describes dimming of his vision over the past two weeks with a sepia tinge. On examination, there is mild voluntary guarding of the abdomen but no discrete masses and no organomegaly. The cardiorespiratory examination is normal. Examination of the neurological system reveals distal weakness with MRC power grade 4/5 in all limbs but normal proximal power. There is a mild tremor present with his arms outstretched and trunk ataxia. Sensory examination discloses painful paraesthesia in the hands and feet with hyperalgesia. There is a loss of proprioception. The cranial nerves are notable in that a left sixth nerve palsy is present with accompanying diplopia. Visual acuity is reduced to 6/30 bilaterally and eye movements are painful. He has a bilateral ptosis. He is noted to have minimal body hair, including hairless arms and legs, lateral third of the eyebrow and temporal and crown baldness which he tells you occurred in the past month. He also has scaling of the palms and soles, tender glossitis and transverse white lines on all his nails. He is cyclothymic during assessment.

What is the most appropriate management for this patient?

[High dose IV hydrocortisone 200mg three times daily](#)[6%High dose IV vitamin B complex \(Pabrinex I+II\) and folic acid](#)[25% Intravenous immunoglobulins](#)[11%Oral Prussian Blue](#)[10g twice daily](#)[45%Procaine penicillin \(G\) 2 million unit daily IM with oral probenidol](#)[13%](#)

Thallium poisoning is a rare cause of painful polyneuropathy, mood change and alopecia.

Treatment is chelation therapy with oral Prussian Blue

The above clinical descriptor is classical for thallium poisoning. The triad of fluctuating mood, with or without confusion, painful distal paraesthesia and alopecia is virtually pathognomonic of toxicity with this heavy metal.

Thallium is a highly toxic metal; in its univalent  $Tl^+$  ion it is readily soluble in water and easily enters the body across the skin or gastrointestinal tract using potassium influx channels. Thallium fumes may also be generated on heating this metal and these may be inhaled when using it during many electroplating manufacturing processes. In the UK, the Health and Safety Executive stipulates that worker occupational exposure limits to thallium in any form must not exceed  $0.1mg/m^3$  in an 8 hour period without adequate ventilation due to the health risks.

Thallium avidly binds to sulphur ligands within cellular proteins, disrupting many intracellular metabolic processes. In massive exposure, death from neuromuscular respiratory failure is rapid, but in more prolonged exposure insidious symptoms of neuropathy, abdominal pain, gastrointestinal bleeding, optic neuritis, confusion and weakness occur. Skin changes such as palm and sole scaling, stomatitis, glossitis, keratitis, eczema and classical alopecia and Mee's lines on the nails typically occur within two weeks of continual exposure. Treatment is with Prussian Blue which is administered orally at a dose of 250-300mg/kg/day (approximately 10g twice daily for an adult) and this complexes with thallium and is excreted in the faeces. Thallium poisoning is often diagnosed late or not at all due to a low index of suspicion; indeed it is often misdiagnosed as Guillain-Barre syndrome due to the glove and stocking distribution of sensory symptoms and patients may receive intravenous steroids or immunoglobulins unnecessarily. In Guillain-Barre syndrome (GBS), classically there is ascending paralysis that is not seen in thallium poisoning and typically sensory symptoms in GBS are of numbness not hyperalgesia.

Thallium poisoning has also been mistaken for neurosyphilis and severe vitamin B deficiency. While neurosyphilis shares symptoms of confusion, fluctuating mood and palmar lesions as well as neuropathy, abdominal symptoms are usually not present and the diagnostic alopecia is absent in syphilis. Similarly, conditions such as Pellagra (niacin deficiency) and beriberi (thiamine deficiency) may share similar features with thallium poisoning such as alopecia, skin changes and mood disturbances, a painful neuropathy is less common; indeed sensory loss is more common in the extremities. Also in these conditions, the prime pathological aetiology is dietary deficiency and the history gives no suggestion this is an issue in this case.

## **Thallium poisoning**

### **Features**

- painful polyneuropathy
- mood change
- alopecia

Treatment is chelation therapy with oral Prussian Blue

### **Question 3 of 49**

A 72-year-old woman attends rheumatology clinic for review of her osteoporosis treatment. She had been diagnosed with osteoporosis five years previously on the basis of a DEXA scan (see results below).



At that time, the DEXA scan had been arranged by her GP due to a strong family history of osteoporosis (maternal hip fracture) and the patient having received multiple courses of corticosteroids as treatment for asthma. The patient has never sustained a fracture of her hip, wrist or vertebrae. Following the initial diagnosis, the patient had been treated with alendronic acid 70 mg weekly. She had not experienced any adverse effects from this medication although reported finding the need to drink copious water with her dose onerous.

The patient's past medical history was significant for asthma, although the patient reported that this was now much better controlled than previously and she had not required any corticosteroid treatment in several years. She denied any history of thyroid disease or rheumatoid arthritis. The patient had never smoked and very rarely consumed any alcohol.

Details from the patient examination in clinic and selected results from her DEXA scans are given below.

Height	160 cm
Weight	65 kg
Femoral neck BMD (5 years previously)	T -2.6 g / cm <sup>2</sup>
Femoral neck BMD (present day)	T -1.9 g / cm <sup>2</sup>
FRAX 10-year probability of major osteoporotic fracture 18 %	
FRAX 10-year probability of hip fracture	6.8 %

What is the most appropriate management of the patient's osteoporosis?

[Discontinue alendronic acid and initiate treatment with denosumab10%](#)[Hold further osteoporosis treatment with repeat DEXA scan in two years43%](#)[Continue treatment with alendronic acid with repeat DEXA scan in five years16%](#)[Continue treatment with alendronic acid with repeat DEXA scan in two years22%](#)[Hold further osteoporosis treatment with repeat DEXA scan in five years9%](#)

At the present time it is uncertain how long patients should take bisphosphonates. Recent concerns about side effects of long-term bisphosphonate treatment (for example, atypical femur fractures) have led to recommendations about the use of treatment breaks ('drug holidays') in certain patients.

The patient in this example meets the recommended criteria for a treatment break. In particular, her age (< 75 years), femoral neck bone mineral density > -2.5 and lack of history of fragility fracture are all favourable. A repeat DEXA scan is recommended after two years or in the event of fragility fracture to review need for further treatment.

It is recommended to use the WHO Fracture Risk Assessment Tool (FRAX) to estimate a patient's 10-year risk of fragility fracture. This can be combined National Osteoporosis Guideline Group (NOGG) guidance

to inform treatment decisions. In this example, the patient's FRAX score would place her below the treatment threshold of NOGG guidance. It should be noted, that despite the recommendation to use FRAX score and NOGG guidance in this situation, neither tools are validated for patients taking bisphosphonates.

Parenteral treatments for osteoporosis such as denosumab should be reserved for individuals in whom bisphosphonate treatment has failure, or who are intolerant of bisphosphonates.

Paskins Z, Warburton L. Bisphosphonates beyond five years. BMJ 2016;352:i264.

<https://www.shef.ac.uk/FRAX/tool.jsp>

## **Osteoporosis: management**

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of - 2.5 SD or below). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- alendronate is first-line
- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

### **Treatment criteria for patients not taking alendronate**

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patient's age, their T-score and the number of risk factors they have from the following list:

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- the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
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- the strictest criteria are for denosumab

### **Supplementary notes on treatment**

#### **Bisphosphonates**

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

#### **Vitamin D and calcium**

- poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

#### **Raloxifene - selective oestrogen receptor modulator (SERM)**

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

## Strontium ranelate

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- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- increased risk of cardiovascular events: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- increased risk of thromboembolic events: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

## Denosumab

- human monoclonal antibody that inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

## Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

## Hormone replacement therapy

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
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## Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

### Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients



© Image used on license from [Radiopaedia](#)



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

A 66-year-old gentleman was admitted for an elective aortic valve replacement. His past medical history included a non-ST elevation myocardial infarction three years prior, as well as hypertension and hypercholesterolaemia. He also suffered a deep vein thrombosis 16 years ago after open reduction and internal fixation of a tibial fracture requiring treatment with warfarin postoperatively. There was no family history of note. He was currently taking aspirin 75mg OD, clopidogrel 75mg OD, ramipril 5mg OD, bisoprolol 2.5mg OD, atorvastatin 20mg ON and lansoprazole 15mg OD.

Two days prior to the operation the patient was commenced on an intravenous heparin infusion which was continued perioperatively. The operation was deemed successful and the infusion was discontinued. He was commenced on enoxaparin 40mg OD sc as prophylaxis for venous thromboembolism postoperatively. He was otherwise making a good post operative recovery and was already mobilising readily. He complained of no chest pain or shortness of breath with no syncopal episodes. He resumed a full and normal diet and his bowel habits were normal. There was no evidence of bleed or any other adverse symptoms.

Routine post operative bloods at day 5 were as follows:

Hb	110 g/l
MCV	81 fl
Haematocrit	0.36
Platelets	$28 \times 10^9/l$
WBC	$9.0 \times 10^9/l$
PT	36 seconds
APTT	86 seconds
D-dimer	136 ng/mL
Fibrinogen	236 g/L

Na <sup>+</sup>	142 mmol/l
K <sup>+</sup>	4.5 mmol/l
Urea	6.3mmol/l
Creatinine	77 $\mu$ mol/l
Bilirubin	17 $\mu$ mol/l
ALP	101 u/l
ALT	16 u/l
Albumin	39 g/l

Blood tests at day 2 were as follows:

Hb	116 g/l
Platelets	$161 \times 10^9/l$
WBC	$10.0 \times 10^9/l$

What is the single most appropriate management step?

[Stop heparin and commence treatment with vitamin K](#)5%[Continue with enoxaparin](#) 9%[Stop all anticoagulation until platelet count is  \$>100 \times 10^9/l\$](#) 11%[Stop enoxaparin and commence danaparoid](#)68%[Stop enoxaparin and commence warfarin](#)7%

The diagnosis is strongly suggestive of heparin induced thrombocytopenia type 2, given the treatment with intravenous heparin, the platelet count in the absence of other haematological abnormalities, the absence of clinical signs of haemorrhage and the onset of low platelet count at day 5 post operatively. This patient is at very high risk of an arterial or venous thrombotic event and needs urgent anticoagulation. Warfarin should not be used alone and there is a 10% cross-reactivity with LMWH, and so of the options available anticoagulation with danaparoid is the most suitable option.

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	Standard heparin	Low molecular weight heparin (LMWH)
<b>Administration</b>	Intravenous	Subcutaneous
<b>Duration of action</b>	Short	Long
<b>Mechanism of action</b>	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, Xla and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
<b>Side-effects</b>	Bleeding Heparin-induced thrombocytopenia (HIT) Osteoporosis	Bleeding Lower risk of HIT and osteoporosis with LMWH
<b>Monitoring</b>	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
<b>Notes</b>	Useful in situations where there is a	Now standard in the management of

<b>Standard heparin</b>	<b>Low molecular weight heparin (LMWH)</b>
high risk of bleeding as anticoagulation can be terminated rapidly	venous thromboembolism treatment and prophylaxis and acute coronary syndromes

#### Heparin-induced thrombocytopenia (HIT)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

#### Question 5 of 49

You are looking after a 76-year-old man on an orthogeriatric ward. He is day 7 post dynamic hip screw for neck of femur fracture. He appears to be doing relatively well, but the nurse has noticed that he has a dark black necrotic looking skin over his left iliac fossa, and has asked you to come and look at it.

His past medical history includes hypertension, mild chronic kidney disease and atrial fibrillation.

He is currently on Ramipril 2.5mg once daily, Bisoprolol 5mg once daily, and treatment dose Clexane (patient was on Warfarin pre-operatively).

Pre-admission operative bloods:

Hb 142 g/l  
Platelets  $212 \times 10^9/l$   
WBC  $14.1 \times 10^9/l$



Na<sup>+</sup> 138 mmol/l  
 K<sup>+</sup> 4.6 mmol/l  
 Urea 8.2 mmol/l  
 Creatinine 167 µmol/l

Bloods yesterday:

Hb 112 g/l  
 Platelets 27 \* 10<sup>9</sup>/l  
 WBC 10.1 \* 10<sup>9</sup>/l

Na<sup>+</sup> 136 mmol/l  
 K<sup>+</sup> 4.0 mmol/l  
 Urea 9.1 mmol/l  
 Creatinine 182 µmol/l

What should you do with regards to his Clexane?

[Stop Clexane and give Warfarin \(target INR 2-3\)10%](#)  
[Stop Clexane and give treatment dose Argatroban58%](#)  
[Switch treatment dose Clexane to Unfractionated Heparin infusion18%](#)  
[Give 1 pool of platelets9%](#)  
[Switch treatment dose Clexane to prophylactic Clexane5%](#)

This is a case of heparin induced thrombocytopenia

Criteria	2	1	0
Thrombocytopenia	>50% fall, and nadir >20*10 <sup>9</sup> /l	30-50% fall, or nadir 10-19*10 <sup>9</sup> /l	fall < 30%, or nadir < 10*10 <sup>9</sup> /l
Timing of platelet fall	Between 5-10 days, or <1 day if exposure to heparin within last 20 days	consistent with immunisation, unclear due to missing samples	fall <4 days after exposure (with no recent exposure history)
Sequelae	Thrombosis, skin necrosis or systemic reaction post-bolus	Progressive or recurrent thrombosis, suspected but unproven thrombosis, erythematous skin reaction	
Alternative cause	None	Possible	Definite

0-3 - Low  
 4-5 - Intermediate  
 6-8 - High

This patient fits all the criteria for heparin induced thrombocytopenia

The recommendations for treatment are as follows:

- Therapeutic danaparoid should be used
- The anticoagulant effect of danaparoids can be measured with anti-Xa assay
- Therapeutic dose fondaparinux is an acceptable alternative anticoagulant (although it is unlicensed)
- Therapeutic anticoagulation should be continued for 3 months (in those with thrombosis) and 4 weeks (in those without thrombosis)
- When transitioning from argatroban to warfarin, the INR should be  $>4$  for 2 days prior to discontinuing argatroban
- Warfarin should not be used till platelet count is back in normal range

British Society of Haematology:

<http://onlinelibrary.wiley.com/doi/10.1111/bjh.12059/epdf>

## Heparin

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	<b>Standard heparin</b>	<b>Low molecular weight heparin (LMWH)</b>
<b>Notes</b>	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

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Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

#### Question 6 of 49

A 73-year-old woman attends rheumatology clinic for review of her osteoporosis treatment. The patient had been diagnosed with osteoporosis five years previously on a DEXA scan performed after she had sustained a fractured right neck of femur. Since the time of diagnosis, the patient had been receiving treatment with alendronic acid (70 mg weekly).

During clinic review, the patient reported taking her alendronic acid as prescribed without any associated side effects. A review of her past medical history revealed that the patient had sustained a left distal radius fracture the previous year following a trip at home. In addition, the patient had suffered from a deep vein thrombosis in her right leg three years before precipitated by a trans-continental flight and had been anti-coagulated with warfarin for six months.

The patient was a smoker (10 cigarettes per day) and also consumed around 20 units of alcohol per week. Her mother had suffered a fractured neck of femur at the age of 80. The patient had never been diagnosed with rheumatoid arthritis and had no significant exposure to corticosteroid treatment.

Clinical examination of the patient demonstrated no loss of height since previous measurement five years previously. There was no tenderness on palpation of the thoracic or lumbar spine.

Height	175 cm
Weight	95 kg
Femoral neck BMD (5 years previously)	T - 2.7
Femoral neck BMD (present day)	T - 2.9
FRAX 10-year probability of major osteoporotic fracture	60 %
FRAX 10-year probability of hip fracture	50 %

What is the appropriate management of the patient's osteoporosis?

[Stop treatment with alendronic acid and start treatment with denosumab39%](#)[Stop treatment with alendronic acid and start treatment with strontium ranelate16%](#)[Continue treatment with alendronic acid with repeat DEXA scan in five years10%](#)[Continue treatment with alendronic acid with repeat DEXA scan in two years27%](#)[Stop treatment with alendronic acid with repeat DEXA scan in two years8%](#)

Due to her extensive risk factors, the patient is at an extremely high risk of suffering from further fragility fractures and it is essential that she continues with osteoporosis treatment. Bisphosphonate treatment failure is defined as two or more fractures on treatment, or one fracture with a reduction in bone density (as in this patient). Therefore, continuing treatment with alendronic acid is not advisable. Of the alternative treatments listed as possible answers, strontium ranelate is contra-indicated in this patient due to her history of deep vein thrombosis, leading to treatment with denosumab as the most appropriate treatment option.

Due to increasing awareness of complications associated with long-term bisphosphonate treatment, treatment breaks (or 'drug holidays') can be considered for some patient's after five years treatment. Guidelines recommend consideration of treatment breaks for patients less than 75 years old with a femoral neck T-score greater than -2.5 and who are defined as low risk by WHO Fracture Risk Assessment Tool (FRAX) and National Osteoporosis Guideline Group (NOGG) guidelines. When a drug holiday is agreed, advice is to repeat DEXA scan after two years, or sooner in the event of a fracture. Treatment breaks are never recommended if a patient has ever suffered from a vertebral insufficiency fracture.

Paskins Z, Warburton L. Bisphosphonates beyond five years. BMJ 2016;352:i264.

<https://www.shef.ac.uk/FRAX/tool.jsp>

## **Osteoporosis: management**

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of  $-2.5$  SD or below). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- alendronate is first-line
- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

### **Treatment criteria for patients not taking alendronate**

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patient's age, their T-score and the number of risk factors they have from the following list:

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've not included them in the revision notes but they may be found by following the NICE link. The most important thing to remember is:

- the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
- the strictest criteria are for denosumab

## Supplementary notes on treatment

### Bisphosphonates

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

### Vitamin D and calcium

- poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

### Raloxifene - selective oestrogen receptor modulator (SERM)

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

### Strontium ranelate

- 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- increased risk of cardiovascular events: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication

- increased risk of thromboembolic events: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

#### Denosumab

- human monoclonal antibody that inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

#### Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

#### Hormone replacement therapy

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

#### Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

#### Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients



© Image used on license from [Radiopaedia](#)



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

Question 8 of 49

A 52-year-old gentleman presents after hearing a popping sound followed by acute onset right ankle pain. On examination he is unable to plantar flex his right ankle. He denies any recent strenuous exercise. He has never had any joint problems but does tell you he has recently been treated for a urinary tract infection. Which one of these antibiotics is likely have contributed to his presentation?

[Erythromycin6%](#) [Trimethoprim6%](#) [Nitrofurantoin12%](#) [Ciprofloxacin71%](#) [Co-amoxiclav5%](#)



A rare side effect of ciprofloxacin is tendon inflammation +/- tendon rupture as listed in the BNF. With a history suggestive of tendon rupture remember to ask about recent antibiotic usage.

<https://www.medicinescomplete.com/mc/bnf/current/PHP3665-ciprofloxacin.htm#PHP56148-sideEffects-topic>

## Quinolones

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature. Examples include:

- ciprofloxacin
- levofloxacin

Mechanism of action

- inhibit topoisomeras II (DNA gyrase) and topoisomerase IV

Mechanism of resistance

- mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration

Adverse effects

- lower seizure threshold in patients with epilepsy
- tendon damage (including rupture) - the risk is increased in patients also taking steroids
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children
- lengthens QT interval

A 24-year-old man with a history of depression and self-harm is brought to the emergency department by a friend 2 hours after an impulsive overdose of ferrous sulphate. He weighs 65kg and has ingested 65 x 200mg ferrous sulphate tablets. This is equivalent to 4225mg of elemental iron (65mg/kg).

On assessment, he denies any abdominal pain, diarrhoea or vomiting.

Observations are as follows:

- Temperature 36.5
- Respiratory rate 18/min
- Saturations 98% on air
- Heart rate 82bpm
- Blood pressure 136/74 mmHg

Venous blood results show:

Hb	133 g/l	Na <sup>+</sup>	139 mmol/l	Bilirubin	8 µmol/l
Platelets	287 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.1 mmol/l	ALP	89 u/l
WBC	8.3 * 10 <sup>9</sup> /l	Urea	3.4 mmol/l	ALT	34 u/l
Neuts	4.2 * 10 <sup>9</sup> /l	Creatinine	72 µmol/l	Albumin	40 g/l
Lymphs	1.3 * 10 <sup>9</sup> /l			Serum iron	70 umol/l
Eosin	0.2 * 10 <sup>9</sup> /l			pH	7.40

Abdominal x-ray demonstrates the presence of iron in the stomach.

What is the appropriate initial medical management

[Whole bowel irrigation31% Activated charcoal20% Emergency endoscopy for removal of iron from the stomach14% Observe and repeat iron levels 4-6 hours after ingestion7% Administer desferrioxamine28%](#)

## Iron overdose

Iron overdose is potentially very serious. Major complications that can occur include:

- Metabolic acidosis

- Erosion of gastric mucosa
- GI bleeding
- Shock
- Hepatotoxicity and coagulopathy

Management is guided by the total amount of iron ingested (elemental iron/kg) and the presence/absence of symptoms (abdominal pain, diarrhoea, vomiting, lethargy).

Patients who have ingested less than 40mg/kg elemental iron and are asymptomatic can be observed at home.

Patients who have ingested > 40mg/kg elemental iron or who are symptomatic need medical assessment with serum iron levels measured 2-4 hours post-ingestion and abdominal x-ray.

Whole bowel irrigation is the decontamination procedure of choice and is performed on all patients presenting within 4 hours who have ingested > 60mg/kg elemental iron or have undissolved tablets on abdominal x-ray.

Activated charcoal is ineffective in iron poisoning.

Desferrioxamine is indicated in:

- Patients with serum iron level > 90umol/l,
- Patients with serum iron level 60-90umol/l, who are symptomatic or have persistent iron on abdominal x-ray despite whole bowel irrigation
- Any patient with shock, coma or metabolic acidosis

Endoscopy or surgery may be required if whole bowel irrigation is not effective or iron is adhered to the gastric wall.

#### Question 1 of 39

A 20-year-old man is brought to the Emergency Department by the Police with agitation and aggression. He is accompanied by a friend, who says they had been out celebrating his brother's birthday and that the patient may have 'snorted something'.

He recalls the patient complaining of intense nasal pain for some time after he allegedly took the substance, but it soon settled and he seemed in good spirits; talking enthusiastically about seeing vivid lights and waves emanating from the club's speakers. As the night went on, however, he became increasingly disturbed; shouting at other clubgoers and complaining about hearing threatening voices.

On examination, his temperature is 39.2°C. His pulse is 117bpm and his blood pressure is 181/98mmHg. He is difficult to examine due to intermittent aggression, and he has lashed out on several occasions.

In order to ensure his own safety, a decision to sedate the patient is made. The patient is successfully restrained and cannulated but suffers a tonic-clonic seizure shortly afterward. He is given 4mg IV lorazepam, but then suffers a cardiac arrest from which he cannot be resuscitated.

Which drug is most likely to be responsible?

[Lysergic acid diethylamide \(LSD\)33%Nexus \(2CB\)24%Spice12%Gamma-hydroxybutyric acid \(GHB\)17%Methoxetamine14%](#)

Nexus is a designer drug belonging to the 2C family; a group of ring-substituted phenethylamines similar in structure to 3,4-methylenedioxy-N-methylamphetamine (MDMA). 2C refers to the presence of two carbon atoms between the amine group and the benzene ring in the chemical structure.

Common features of 2C intoxication include agitation, aggression, and hallucinations, often complicated by the presence of serotonergic or sympathomimetic toxidromes. It is possible to increase the hallucinogenic effects of these drugs by placing substituents on the aromatic ring at positions 2, 4, or 5. Synthesis of 2C drugs by amateur chemists can, therefore, lead to the inadvertent formation of dangerously potent agents.

2Cs are ingested orally or by insufflation, with the latter being extremely painful. At low doses, 2Cs have stimulating effects and cause increased visual, auditory and tactile sensations. Hallucinations occur at moderate doses, whilst high doses can cause frightening hallucinations, hypertension, tachycardia, hyperthermia, seizures and excited delirium.

Patients with excited delirium often exhibit aggression, hyperactivity, hyperthermia and, as in this case, unexpected cardiac arrest. It is thought to relate to excessive dopamine release in the mesolimbic pathways and has been linked to a number of 2C-related deaths.

LSD is also a hallucinogen, but it would not cause the hypertension or hyperthermia evident in the vignette. Fatal overdose is rare.

GHB is a CNS depressant that causes euphoria followed by coma. It has a short duration of action and toxicity is often maximal at presentation.

Methoxetamine is a ketamine derivative that causes dissociative symptoms, tachycardia, hypertension, confusion, and occasionally an acute cerebellar syndrome. It does not typically cause hallucinations.

Spice is a synthetic cannabinoid. Like marijuana, spice is usually smoked or ingested orally. Intoxication results in elevated mood, relaxation, and altered perception. Spice, however, is more likely than marijuana to cause hypertension, tachycardia, seizures and acute psychosis.

## **Novel psychoactive substances**

Novel psychoactive substances is the medical term for the many new substances which are chemically related to established recreational drugs such as MDMA and cannabis. They are often referred to as 'legal highs' although this is a misnomer in the UK, as their distribution and sale have been illegal since 2016.

The information below describes some of the common types:

### **Stimulants**

- similar to MDMA, amphetamines and cocaine, resulting in increased levels of serotonin, dopamine and noradrenaline, resulting in a 'high' and feeling of euphoria
- a common example is a stimulant NPS is mephedrone ('bath salts', 'M-CAT', 'meow meow'). It is a cathinone and structurally similar to khat, a plant found in East Africa
- another example is benzylpiperazine ('Exodus', 'Legal X', 'Legal E')
- typically swallowed as a pill/powder ('bombing') or snorted
- adverse effect profile similar to MDMA/cocaine, with the risk of serotonin syndrome

### **Cannabinoids**

- termed synthetic cannabinoid receptor agonists
- commonly referred to as 'spice'
- typically sprayed on to herbal mixtures which are then smoked. Also available in liquid form which is then inhaled using e-cigarettes
- similar adverse effects to cannabis

### **Hallucinogenics**

- can be either dissociatives and psychedelics
- dissociatives produce a similar effect to ketamine, with a sense of not being connected to the physical body or time. A common dissociative NPS is methoxetamine ('mexxy')
- psychedelics have a similar effect to LSD although NPS versions may also be a stimulant

### **Depressant**

- can be either opioid or benzodiazepine-based
- usually taken as a pill or a powder

- often structurally very similar to the original drug class, hence the adverse effects are similar
- benzodiazepine NPS often have a significantly longer half-life

Other substances include:

- Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL): 'G', 'Geebs' or 'Liquid Ecstasy'
- Nitrous oxide: 'Hippie crack'

For a more detailed overview please see the excellent review in BMJ 2017;356:i6848

### Question 3 of 39

A 29-year-old male from Eastern Europe presents to the Emergency Department with 48 hours of severe 'burning and sharp' electrical pains in his arms and legs. He is well known to the department, having been treated for alcohol withdrawal a number of times in the past and is a known intravenous drug user. He reports no weakness, dysarthria or hallucinations. He reports drinking about 7 pints of beer in the past 24 hours, which he says is normal for him, and has used intravenous heroin daily for the past 2 weeks.

On examination, both upper and lower limbs are rigid and mildly bradykinetic. A bilateral resting tremor is noted in both hands. Reflexes and sensation are normal. Examination of cranial nerves and eye movements are unremarkable.

His initial blood tests return and are as follows:

Hb	163 g/l
Platelets	276 * 10 <sup>9</sup> /l
WBC	5.5 * 10 <sup>9</sup> /l
Vitamin B12	202 ng/l
Folate	471 (>317 nmol/l)

Na <sup>+</sup>	142 mmol/l
K <sup>+</sup>	4.3 mmol/l
Urea	6.4 mmol/l
Creatinine	85 µmol/l
CRP	7mg/l
HIV	negative

Which investigation is most likely to yield the underlying diagnosis?

[DAT scan13%](#)[Anti-GM1b antibodies11%](#)[Borrelia burgdorferi serology10%](#)[Urine porphobilinogen15%](#)[Serum heavy metals51%](#)

The patient has presented with extrapyramidal signs in the context of a HIV-negative intravenous drug user with alcohol excess. The differential causes for Parkinsonism should be considered: idiopathic, genetic, trauma, vascular etc.

Urinary porphobilinogen is a diagnostic test for acute intermittent porphyria (AIP), typically presenting with significant abdominal pain, urinary symptoms and a peripheral neuropathy. Anti-GM1b are antibodies typically present in multifocal motor neuropathy with conduction block, an immune disorder affecting motor peripheral nerves alone. Heavy metal poisoning must be considered in a young patient with Parkinsonism, in addition to the MPTP toxins found in classic cases of intravenous drug users in 1980s California. This patient is vulnerable to metals such as manganese, which is often found in 'dirty' preparation of intravenous heroin from Eastern Europe and produces extrapyramidal symptoms similar to idiopathic Parkinson's disease. Similar symptoms should be suspected in heavy industry workers.

## Heavy metal poisoning

### Causes

- lead: most common
- mercury
- manganese
- cadmium
- thallium

### Question 4 of 39

A 48-year-old female presented with general fatigue, and nausea. She denies having pyrexia, vomiting diarrhoea or any pains. She appeared dehydrated but otherwise, observations and physical examination were within normal limits.

Blood results are as follows:

Na<sup>+</sup> 130 mmol/l  
K<sup>+</sup> 4.8 mmol/l  
Urea 18 mmol/l  
Creatinine 162 µmol/l  
Lithium 1.6 mmol/l (0.4-1.0 mmol/l)

Looking back at past results from 3 weeks ago, her renal function was in the normal range.

She has a history of bipolar disorder, diet-controlled diabetes and hypertension. She has been compliant with her lithium tablets and undergoing regular checks for the levels.

The patient revealed that her General Practitioner had recently started her on a new tablet 2 weeks ago.

Which of the following would most likely be the precipitant for her symptoms?

[Indapamide54%Amlodipine9%Dihydrocodeine6%Spironolactone19%Propranolol12%](#)

Acute renal impairment and lithium toxicity can be precipitated by any medicines that can impair renal function or induce hyponatraemia:

- Angiotensin-converting enzyme (ACE) inhibitors
- Diuretics (particularly thiazides including bendroflumethiazide and indapamide)
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Target concentrations of lithium:

- acute episode (mania, hypomania, depression) 0.6-1.0 mmol/L (elderly 0.4-0.8 mmol/L).
- prophylaxis of bipolar affective disorder 0.4-0.8 mmol/L.
- toxic range usually >1.5 mmol/L; however, may begin at >1.0 mmol/L (levels >2 mmol/L need urgent treatment).

## **Lithium toxicity**

Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys. Lithium toxicity



generally occurs following concentrations > 1.5 mmol/L.

Toxicity may be precipitated by dehydration, renal failure, diuretics (especially bendroflumethiazide), ACE inhibitors, NSAIDs and metronidazole.

#### Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- seizure
- coma

#### Management

- mild-moderate toxicity may respond to volume resuscitation with normal saline
- haemodialysis may be needed in severe toxicity
- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion

#### Question 6 of 39

A 28-year-old woman was admitted to the Emergency Department drowsy and unwell after a suspected suicide attempt at home. The patient was under the care of the community psychiatry and had been receiving treatment for schizoaffective disorder. There was no other known past medical history. The paramedics bringing the patient to hospital also had brought the medications they found in the patient's home including quetiapine, levomepromazine, zopiclone and oxazepam. The paramedics reported that they had not seen evidence of empty medication packets or blister packs at the patient's home.

Initial assessment of the patient was unremarkable except for reduced consciousness level. Basic observations at presentation are listed below.

- Blood pressure: 150/79 mmHg
- Heart rate: 89 bpm
- Respiratory rate: 20 / min
- O2 saturations (15 L O2): 100 %
- Glasgow coma score: M5 V3 E2
- Blood glucose: 7.0 mmol / L
- Temperature: 36.8°C

Results from an arterial blood sample (15 L O2) were as follows.

pH            7.19

PaCO<sub>2</sub> 3.3 kPa  
PaO<sub>2</sub> 21.2 kPa  
Bicarbonate 8.9 mmol / L (reference 20.0-26.0)

Sodium 142 mmol / L  
Potassium 3.6 mmol / L  
Calcium 2.13 mmol / L (reference 2.20-2.60)  
Chloride 110 mmol / L (reference 99-108)  
Urea 5.2 mmol / L  
Creatinine 110 micromol / L  
Lactate 26 mmol / L  
Plasma osmolality 380 mmol / Kg (reference 280-295)  
Haemoglobin 12.0 g / dL

Based on the above blood results, what is the most likely cause of the patient's reduced consciousness level?

[Ethanol intoxication13%](#)[Benzodiazepine overdose8%](#)[Ethylene glycol intoxication62%](#)[Quetiapine overdose15%](#)[Chronic renal failure3%](#)

The patient is unwell with a severe lactic acidosis. However, there is no clinical evidence for conditions that may cause this state (such as shock, hypoxia, sepsis or lactate-inducing drugs). Calculation of the anion gap and osmolality gap provide further clues to the likely cause.

Anion gap = Sodium - (Chloride + Bicarbonate) = 23.1 mmol / L (reference 5-11)

Osmolality gap = Measured osmolality - ((2\*Sodium) + Urea + glucose)) = 83.8 mmol / Kg (reference < 6)

A severe lactic acidosis may cause a small osmolality gap (< 10 mmol / Kg) but is not consistent with the high value in this case). Possible causes of a high osmolality gap include pseudohyponatraemia (in extreme hyperproteinaemia or hyperlipidaemia), chronic renal failure or excess of toxic alcohols or glycols.

However, in the case of ethanol intoxication or pseudohyponatraemia the osmolality gap is not associated with a metabolic acidosis. Given that the blood results do not suggest evidence of chronic renal failure, the most likely cause is ethylene glycol intoxication. Testing for serum levels of methanol and ethylene glycol would confirm the diagnosis. Appropriate treatment is with ethanol and haemodialysis.

There is no evidence from the collateral history that the patient had taken an overdose of her prescription medications and this would not explain the metabolic abnormalities.

Oostvogels R, Kemperman H, Hubeek I, ter Braak E. The importance of the osmolality gap in ethylene glycol intoxication. BMJ 2013;347:f6904.

## Ethylene glycol toxicity

Ethylene glycol is a type of alcohol used as a coolant or antifreeze

Features of toxicity are divided into 3 stages:

- Stage 1: symptoms similar to alcohol intoxication: confusion, slurred speech, dizziness
- Stage 2: metabolic acidosis with high anion gap and high osmolar gap. Also tachycardia, hypertension
- Stage 3: acute renal failure

Management has changed in recent times

- ethanol has been used for many years
- works by competing with ethylene glycol for the enzyme alcohol dehydrogenase
- this limits the formation of toxic metabolites (e.g. glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning
- **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol
- haemodialysis also has a role in refractory cases

### Question 7 of 39

A 25-year-old man with a history of ulcerative colitis is seen in the Emergency Department with severe abdominal pain and diarrhoea. He is passing stool 8 times a day with blood.

On admission his temperature is 38.2 °C. His heart rate is 110/min and his blood pressure is 100/62 mmHg. His abdomen is soft but very tender in the the left lower quadrant with normal bowel sounds.

He is started on intravenous fluids, methylprednisolone and antibiotics.

His initial abdominal x-ray shows mural thickening of the descending colon.

His blood and stool culture results show no growth and antibiotics are stopped

After three days his stool frequency is 6 per day with visible blood and he continues to be tachycardic.

The gastroenterology team decide to escalate his therapy by adding in ciclosporin. Which of the following factors would prompt a decision to use infliximab instead?

[Chronic kidney disease45%](#)[Megacolon on abdominal x-ray17%](#)[Previous hepatitis B12%](#)[Previous renal transplant11%](#)[Previous tuberculosis16%](#)

This man has severe ulcerative colitis which is steroid refractory at 72 hours and therefore warrants additional therapy.

The first choice for this is generally ciclosporin. However, in patients with pre-existing chronic kidney disease, ciclosporin is contraindicated.

Previous hepatitis B and previous tuberculosis are both contraindications to infliximab due to risk of reactivation and should be checked prior to starting this.

Megacolon on x-ray would be an indication for urgent surgical review and intervention.

Previous renal transplant patients may already be on immunosuppression and careful multidisciplinary management would be indicated. However, ciclosporin is used as immunosuppression for patients with renal transplant and so this is not a contraindication to its use.

Reference:

National Institute for Health and Care Excellence. Ulcerative colitis: management NICE guidelines [CG166] 2013 .

## **Ciclosporin**

Ciclosporin is an immunosuppressant which decreases clonal proliferation of T cells by reducing IL-2 release. It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a phosphatase that activates various transcription factors in T cells

Adverse effects of ciclosporin (note how everything is increased - fluid, BP, K<sup>+</sup>, hair, gums, glucose)

- nephrotoxicity

- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- tremor
- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection

Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

#### Indications

- following organ transplantation
- rheumatoid arthritis
- psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- ulcerative colitis
- pure red cell aplasia

#### Question 9 of 39

An 85-year-old female is admitted under the general medical unit with acute thoracic back pain from a T6 crush fracture following a fall. She has a past history of systolic heart failure, depression and osteoporosis.

Her regular medications included aspirin, frusemide, spironolactone, bisoprolol, sertraline and calcium, vitamin D and weekly alendronate. These are continued throughout her admission.

Two days into her admission, the nurses note that she is agitated and a bit confused.

On examination, she looks flushed and is tachycardic with a heart rate of 120 beats/min and is hypertensive with a blood pressure of 185/70 mmHg, but is afebrile. Both her pupils are mildly dilated, she is mildly tremulous and is noted to have deep tendon hyperreflexia with easily inducible clonus.

Use of which of the following analgaesic medication could explain her current symptoms?

[Paracetamol4%](#)[Ibuprofen12%](#)[Oxycodone18%](#)[Tramadol45%](#)[Hydromorphone22%](#)

Serotonin syndrome is a disorder characterised by serotonin excess, usually due to the use of 2 or more serotonergic drugs. Manifestations of the syndrome include changes in mental status, neuromuscular changes and autonomic overactivity. Clinically, this can be observed as hypertension, tachycardia, flushing and sweating, hyperflexia, clonus and muscle rigidity. Other potential signs include fever and changes in mental status, including agitation.

Serotonergic drugs that are associated with serotonin syndrome include tramadol, selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), triptans and St Johns wort.

The management of serotonin syndrome involves discontinuation of all serotonergic drugs and supportive care. If required, benzodiazepine can be administered to control agitation. In moderate to severe cases, 5-HT antagonists (e.g. cyproheptadine and chlorpromazine) are sometimes administered.

#### References:

- Hall M, Buckley N. Serotonin Syndrome. Aust Prescr. 2003;26:62-3
- Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005 Mar 17;352(11):1112-20.

## **Serotonin syndrome**

### Causes

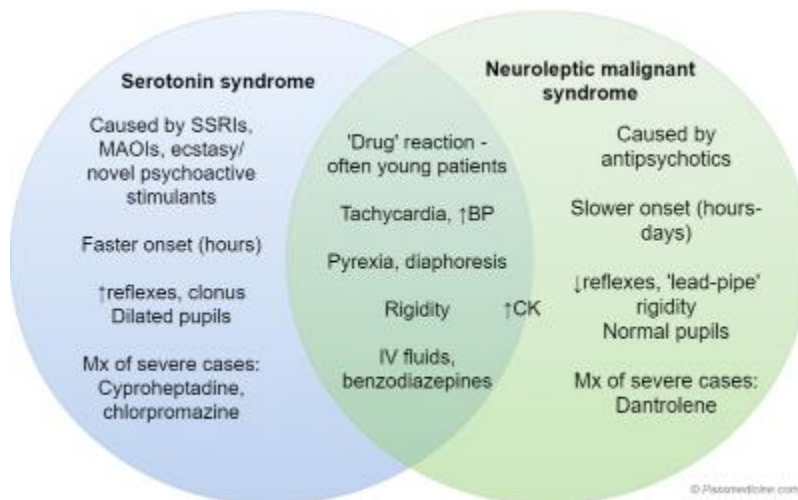
- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines

### Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state

## Management

- supportive including IV fluids
- benzodiazepines
- more severe cases are managed using serotonin antagonists such as cyproheptadine and chlorpromazine



Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

### Question 2 of 30

A 25-year-old female was admitted to the emergency department following an overdose of unknown tablets 4 hours ago. Her past medical history includes depression, previous overdoses and gastric ulcer disease. On examination, she was drowsy but easily rousable with a Glasgow Coma Score of 14. She has a heart rate of 112 beats per minute, blood pressure of 106/60mmHg, respiratory rate of 22 and saturations of 96% on air.

Electrocardiogram shows a sinus tachycardia with QRS complexes measuring 160 ms.

An arterial blood gas on air revealed the following results:

pH 7.29  
pCO<sub>2</sub> 6.2 kPa  
pO<sub>2</sub> 10.5 kPa

HCO<sub>3</sub><sup>-</sup> 18 mmol/l  
BE -6.6 mmol/l

Which of the following management is the most appropriate?

[Intravenous magnesium9% Activated charcoal5% Gastric lavage5% Sodium bicarbonate76% 5% dextrose infusion5%](#)

Tricyclic Antidepressant (TCA) overdose is most likely in this case, based on the presentation, mixed acidosis seen on ABG and ECG changes. TCA overdose can present in various ways. Cardiovascular effects include tachycardia, prolong QRS complexes and induce cardiac arrhythmias. Central nervous system effects include altered mental status, coma and seizures.

- Intravenous magnesium: no indications in this case of TCA overdose
- Activated charcoal: only appropriate if GCS is not reduced and if patients present within 2 hours of ingestion
- Gastric lavage: may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1h of ingestion and the airway is protected
- Sodium bicarbonate: is the main treatment for dysrhythmias or hypotension associated with TCA overdoses
- 5% dextrose infusion: has no role in treatment of TCA poisoning or fluid resuscitation

Source: Guidelines in Emergency Medicine Network (GEMNet): guideline for the management of tricyclic antidepressant overdose

## Tricyclic overdose

Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and doxepin (dothiepin) are particularly dangerous in overdose.

Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- arrhythmias
- seizures
- metabolic acidosis
- coma



ECG changes include:

- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

### Management

- IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics

### Question 3 of 30

A 74-year-old woman attends rheumatology clinic for a review of her osteoporosis treatment. The patient had been diagnosed with osteoporosis on a DEXA scan five years previously after she fell and sustained a Colles fracture on the left side. Following this diagnosis, the patient had been initiated on treatment with alendronic acid.

In clinic, the patient reported that she had recently been suffering from nagging back pain over the past few weeks. She denied any history of recent falls or other trauma.

Past medical history was significant for rheumatoid arthritis, diagnosed when the patient was 28 years old. Following this diagnosis, she had received prolonged treatment with corticosteroids in association with a variety of disease modifying drugs. Ultimately, good control of her arthritis had been achieved using methotrexate (10 mg weekly) and the patient had not required corticosteroid treatment for many years. The patient reported no family history of osteoporosis or fragility fractures. She did not smoke or drink any alcohol.

The patient reported no concerns or side effects associated with taking her weekly alendronic acid (70 mg weekly).

Examination of the patients spine demonstrated mid-line point tenderness around the T12 - L1 level.

Neurological examination of the lower limbs was unremarkable.

Thoracolumbar spine x-ray: anterior height loss of T12 vertebrae, otherwise unremarkable

Height	150 cm
--------	--------

Weight	55 kg
--------	-------

Femoral neck BMD (5 years previously)	T - 3.2
---------------------------------------	---------

Femoral neck BMD (present day)	T - 2.4
--------------------------------	---------

FRAX 10-year probability of major osteoporotic fracture 27 %

FRAX 10-year probability of hip fracture	8.7 %
--	-------

What is the most appropriate management of the patient's osteoporosis?

[Hold further osteoporosis treatment with repeat DEXA scan in two years21%](#)[Hold further osteoporosis treatment with repeat DEXA scan in five years5%](#)[Discontinue alendronic acid and initiate treatment with denosumab30%](#)[Discontinue alendronic acid and initiate treatment with zoledronic acid7%](#)[Continue treatment with alendronic acid with repeat DEXA scan in five years36%](#)

The patient's bone mineral density has improved secondary to her treatment with alendronic acid. However, her recent back pain and abnormal thoracolumbar x-ray suggest she has suffered from a osteoporotic vertebral fracture. In one study, continuing alendronic acid from five to ten years treatment reduced the incidence of clinical vertebral fractures in all patients regardless of T score. Therefore, continuing alendronic acid treatment would be recommended for this patient.

Due to increased awareness of the potential complications of long-term bisphosphonate treatment, treatment breaks (or 'drug holidays') are now employed for some patients. Specifically, a treatment break should be considered for patients less than 75 years old, with femoral neck T score > - 2.5, no history of osteoporotic vertebral fracture and deemed low risk following assessment by WHO Fracture Risk Assessment Tool (FRAX) and National Osteoporosis Guideline Group (NOGG) guidance. For such a patient, treatment would typically be suspended for two years with repeat DEXA scan at the end of that period, or sooner in the event of fragility fracture.

Parenteral osteoporosis treatments such as zoledronic acid or denosumab should be considered if patient is intolerant of oral bisphosphonates or in the event of treatment failure (defined as two or more fractures on treatment, or one fracture and a fall in bone mineral density).

Paskins Z, Warburton L. Bisphosphonates beyond five years. BMJ 2016;352:i264.

<https://www.shef.ac.uk/FRAX/tool.jsp>

## **Osteoporosis: management**

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of  $-2.5$  SD or below). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- alendronate is first-line
- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

### **Treatment criteria for patients not taking alendronate**

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patient's age, their T-score and the number of risk factors they have from the following list:

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've not

included them in the revision notes but they may be found by following the NICE link. The most important thing to remember is:

- the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
- the strictest criteria are for denosumab

### **Supplementary notes on treatment**

#### **Bisphosphonates**

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

#### **Vitamin D and calcium**

- poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

#### **Raloxifene - selective oestrogen receptor modulator (SERM)**

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

#### **Strontium ranelate**

- 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care

- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- increased risk of cardiovascular events: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- increased risk of thromboembolic events: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

#### Denosumab

- human monoclonal antibody that inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

#### Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

#### Hormone replacement therapy

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

#### Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

#### Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients



© Image used on license from [Radiopaedia](#)



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

#### Question 1 of 27

A 49-year-old woman comes to the Emergency department suffering from nausea and lethargy which has increased over the past few days. She has undergone a renal transplant for end stage renal failure due to chronic reflux nephropathy some 3 months ago. You understand her GP prescribed an antibiotic for a respiratory tract infection without checking for potential interactions with her ciclosporin based immunosuppressive regime. Creatinine has increased significantly, and ciclosporin is above the upper limit of the recommended range.

Investigations:

Na <sup>+</sup>	142 mmol/l
K <sup>+</sup>	5.1 mmol/l
Urea	8.2 mmol/l
Creatinine (3 months ago)	161 µmol/l
Creatinine (today)	225 µmol/l

Which of the following antibiotics is she most likely to have been prescribed?

[Amoxicillin5% Cephalexin5% Clarithromycin66% Doxycycline6% Levofloxacin18%](#)

The key here is to recognise that ciclosporin is metabolised by CYP3A4, and clarithromycin and erythromycin are both potent CYP3A4 inhibitors, leading to a potential elevation in ciclosporin levels, and subsequent nephrotoxicity. Because of the danger of either CYP3A4 inhibition or activation in patients taking ciclosporin, patients are advised to consult their transplant team before starting any new medication.

Amoxicillin is predominantly excreted unchanged in the urine, as is cephalexin. Levofloxacin undergoes very limited biotransformation, with 85% excreted in the urine. Doxycycline is concentrated in bile, not metabolised via the P450 system. After 3 days around 40% is excreted in the urine and approximately 30% in faeces.

## **Ciclosporin**

Ciclosporin is an immunosuppressant which decreases clonal proliferation of T cells by reducing IL-2 release. It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a phosphatase that activates various transcription factors in T cells

Adverse effects of ciclosporin (note how everything is increased - fluid, BP, K<sup>+</sup>, hair, gums, glucose)

- nephrotoxicity
- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- tremor
- impaired glucose tolerance
- hyperlipidaemia

- increased susceptibility to severe infection

Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

#### Indications

- following organ transplantation
- rheumatoid arthritis
- psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- ulcerative colitis
- pure red cell aplasia

#### Question 2 of 27

A 72-year-old man attends rheumatology clinic for review of his osteoporosis treatment after being referred by the orthopaedic team. The patient had been diagnosed with osteoporosis six years previously after a DEXA scan had been arranged by his General Practitioner. Treatment with alendronic acid (70 mg weekly) had been initiated immediately after the diagnosis. After five years of bisphosphonate treatment, a repeat DEXA scan had been arranged and following review in rheumatology clinic, a treatment break had been agreed with the patient. Unfortunately, one year after stopping alendronic acid, the patient had tripped and fractured his right neck of femur, subsequently undergoing hemiarthroplasty.

Other past-medical history was significant for an episode of giant cell arteritis 10 years previously that had necessitated a prolonged course of corticosteroids. However, patient was now successfully weaned from corticosteroid treatment and remained in remission. The patient had never been diagnosed with rheumatoid arthritis and did not smoke cigarettes or drink alcohol. There was no family history of fragility fractures that the patient could recall.

On questioning, the patient reported that he had never had any adverse effects from alendronic acid treatment and would be happy to take this medication again if recommended.

Height 185 cm

Weight 90 kg

Femoral neck BMD (6 years previously) T - 2.7

Femoral neck BMD (1 year previously) T - 2.3



What is the most appropriate next step in the management of the patient's osteoporosis?

[Repeat DEXA scan not required, start treatment with zoledronic acid8%Repeat DEXA scan not required, restart treatment with alendronic acid48%Repeat DEXA scan in one year9%Repeat DEXA scan not required, start treatment with denosumab15%Repeat DEXA scan immediately19%](#)

Due to an increased awareness of the potential harms of long-term bisphosphonate treatment, treatment breaks are considered after five years of bisphosphonate treatment when a patient is aged under 75 years, has a femoral neck T-score greater than - 2.5 and is assessed as being below the treatment threshold based on the WHO Fracture Risk Assessment Tool (FRAX) and National Osteoporosis Guideline Group (NOGG) guidelines.

At the point in time when alendronic acid treatment was held one year previously, the above patient met these criteria with a 10-year probability of major osteoporotic fracture of 8.9 %.

Current recommendation is for an individual on a treatment break to have a repeat DEXA scan after two years or sooner in the event of a fragility fracture. Therefore, the correct answer is to repeat the DEXA scan immediately to allow re-calculation of the patient's osteoporosis risk to inform future treatment decision.

If it is decided to restart treatment then it would be appropriate to return to alendronic acid as this had been well tolerated by the patient and had led to an improvement in bone density. Parenteral treatments such as zoledronic acid or denosumab are employed if oral treatments are not tolerated or in the event of bisphosphonate treatment failure.

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- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients



© Image used on license from [Radiopaedia](#)



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

### Question 3 of 25

A 65-year-old female presents to her GP with a four days history of non-itchy rashes on her face, neck and bilateral upper limbs. Her chest and abdomen are not affected. She does regular gardening. Her past medical history includes myocardial infarction and asthma. Further history reveals that last week she was seen in the cardiology outpatient clinic for arrhythmias and was started on a new medication. Which of the following drug is most likely causing the patient's symptom?

[Digoxin10%](#) [Dabigatran9%](#) [Verapamil8%](#) [Amiodarone67%](#) [Flecainide7%](#)

The distribution of the rash suggests phototoxicity. Among the list of the medications, only amiodarone and flecainide are associated with phototoxicity. However, flecainide is contraindicated in patients with history of myocardial infarction.

### **Amiodarone and the thyroid gland**

Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

#### **Amiodarone-induced hypothyroidism**

The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect\*

Amiodarone may be continued if this is desirable

#### **Amiodarone-induced thyrotoxicosis**

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

	<b>AIT type 1</b>	<b>AIT type 2</b>
Pathophysiology	Excess iodine-induced thyroid hormone synthesis	Amiodarone-related destructive thyroiditis
Goitre	Present	Absent
Management	Carbimazole or potassium perchlorate	Corticosteroids

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT

\*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

#### **Question 4 of 25**

A 64-year-old woman comes to the Emergency department complaining of palpitations at rest, and worsening angina over the past month. She has been treated with amiodarone for the past 3 years for recurrent ventricular tachycardia. She has a blood pressure of 110/70 mmHg, pulse of 95 beats per minute, and a fine tremor. There is no goitre. TSH is suppressed at less than 0.05 U/ml.

You suspect she has amiodarone induced thyrotoxicosis. How best can you determine the underlying pathophysiology?

[IL6 level13% Thyroglobulin level30% TSH level7% Duration of amiodarone therapy7% Colour flow doppler ultrasonography43%](#)

Type 1 amiodarone induced thyrotoxicosis is caused by increased production of thyroid hormone, most likely as a result of the excess iodine load administered to the patient as a result of amiodarone treatment. Type 2 amiodarone induced thyrotoxicosis is caused by a destructive thyroiditis. Colour flow doppler ultrasonography needs to be performed by an experienced operator, but is thought to distinguish between the two causes of amiodarone induced thyrotoxicosis around 80% of the time. In patients where the diagnosis is uncertain, radioiodine uptake, (which is low in type 2 disease) may further help differentiating between the two.

Type 2 disease is generally seen later in the time course of amiodarone therapy, although this isn't an invariable differentiating factor, and data on the usefulness of IL6 and thyroglobulin is conflicting.

Reference on use of colour flow doppler:

<http://www.ncbi.nlm.nih.gov/pubmed/11849244>

## **Amiodarone and the thyroid gland**

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\*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

#### Question 1 of 21

A 48-year-old farmer is found collapsed in his workshop having left a suicide note and consumed unknown weedkillers and insecticides from his store. On arrival in the Emergency department, his Glasgow coma scale is 10, pupils are pinpoint and poorly reactive. His blood pressure is 100/70 mmHg, his pulse is 88 beats per minute and regular. He moans incomprehensibly when you palpate his abdomen. You are concerned about the possibility of a paraquat overdose. How can you screen for it?

[Serum NADPH testing36%](#)[Serum free fatty acid testing8%](#)[Urine copper sulphate testing7%](#)[Urine ketone testing6%](#)[Urine dithionate testing44%](#)

Qualitative confirmation of paraquat in the urine is easily performed in any laboratory. The main role of this test is to confirm or exclude exposure to paraquat. The presence of paraquat is confirmed by a colour change noted after the addition of a dithionite solution. The test is usually positive within six hours of a large ingestion and remains positive for several days. It's important not to wait for the results of the test before administering oral Fuller's earth.

The other options have no value in the evaluation of paraquat poisoning. Serum free fatty acids may rise where there is mitochondrial dysfunction, as may urinary ketones. Serum lactate is used in evaluation of metabolic dysfunction associated with cyanide poisoning.

### Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Treatment
Paracetamol	Management



<b>Toxin</b>	<b>Treatment</b>
	<ul style="list-style-type: none"> <li>• activated charcoal if ingested &lt; 1 hour ago</li> <li>• N-acetylcysteine (NAC)</li> <li>• liver transplantation</li> </ul>
	Management
<b>Salicylate</b>	<ul style="list-style-type: none"> <li>• urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning</li> <li>• haemodialysis</li> </ul>
<b>Opioid/opiates</b>	Naloxone
<b>Benzodiazepines</b>	Flumazenil
	Management
<b>Tricyclic antidepressants</b>	<ul style="list-style-type: none"> <li>• IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity</li> <li>• arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias</li> <li>• dialysis is ineffective in removing tricyclics</li> </ul>
	Management
<b>Lithium</b>	<ul style="list-style-type: none"> <li>• mild-moderate toxicity may respond to volume resuscitation with normal saline</li> <li>• haemodialysis may be needed in severe toxicity</li> <li>• sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion</li> </ul>
<b>Warfarin</b>	Vitamin K, prothrombin complex
<b>Heparin</b>	Protamine sulphate
	Management
<b>Beta-blockers</b>	<ul style="list-style-type: none"> <li>• if bradycardic then atropine</li> <li>• in resistant cases glucagon may be used</li> </ul>
<b>Ethylene glycol</b>	Management has changed in recent times

Toxin	Treatment
	<ul style="list-style-type: none"> <li>ethanol has been used for many years</li> <li>works by competing with ethylene glycol for the enzyme alcohol dehydrogenase</li> <li>this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning</li> <li><b>fomepizole</b>, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol</li> <li>haemodialysis also has a role in refractory cases</li> </ul>
	Management
<b>Methanol poisoning</b>	<ul style="list-style-type: none"> <li>fomepizole or ethanol</li> <li>haemodialysis</li> </ul>
	Management
<b>Organophosphate insecticides</b>	<ul style="list-style-type: none"> <li>atropine</li> <li>the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit</li> </ul>
<b>Digoxin</b>	Digoxin-specific antibody fragments
<b>Iron</b>	Desferrioxamine, a chelating agent
<b>Lead</b>	Dimercaprol, calcium edetate
	Management
<b>Carbon monoxide</b>	<ul style="list-style-type: none"> <li>100% oxygen</li> <li>hyperbaric oxygen</li> </ul>
<b>Cyanide</b>	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate

#### Question 3 of 21

A 23-year-old female student presents to the emergency department with a headache which has developed since starting her third year at university studying economics. She has also been noticing nausea and breathlessness. She had spent the summer travelling to Argentina and teaching English, after which she returned to the UK and moved into shared student accommodation in preparation for her next term. She had been well during her travels except for four days of diarrhoea shortly after she arrived. She has a past medical history of chlamydia

which was treated by a local GUM clinic. She does not smoke and has minimal alcohol intake. On examination, she appears tired but otherwise well. Auscultation of her chest is normal. A urinary pregnancy test is positive.

Blood tests:

Hb 127 g/l  
Platelets  $336 \times 10^9/l$   
WBC  $9.4 \times 10^9/l$   
Na<sup>+</sup> 137 mmol/l  
K<sup>+</sup> 4.2 mmol/l  
Urea 3.7 mmol/l  
Creatinine 63  $\mu$ mol/l

Arterial blood gas:

pH 7.41  
pCO<sub>2</sub> 3.6 mmHg  
pO<sub>2</sub> 9.4 mmHg  
Na<sup>+</sup> 137 mmol/l  
FCOHb 22%

She is started on 15L of oxygen via a non-rebreather mask. How should she be further managed?

[Wean off oxygen guided by standard pulse oximetry saturation levels8%Add IV mannitol5%Maintain high-flow oxygen until asymptomatic or carbon monoxide levels are <10%40%Refer urgently for hyperbaric oxygen treatment42%Arrange urgently for non-invasive ventilation5%](#)

This is a case of carbon monoxide poisoning in a pregnant patient and therefore needs urgent consideration of hyperbaric oxygen treatment. The danger of carbon monoxide poisoning to the foetus is significant as carbon monoxide has greater affinity to foetal haemoglobin and the placenta is unable to substantially compensate for reduced oxygen delivery. Whilst mild to moderate poisoning has not been shown to cause any adverse outcomes, severe maternal poisoning has been shown to cause neurobehavioural deficits when treated with normobaric oxygen alone.

Standard pulse oximetry would be unable to assess oxygenation levels in carbon monoxide poisoning. Whilst if this patient was not pregnant, there would be no indication for hyperbaric oxygen treatment and maintaining high flow oxygen until asymptomatic or carbon monoxide levels would be less than 10% would then be appropriate. Non-invasive ventilation has no role in carbon monoxide poisoning, and mannitol is only indicated in cerebral oedema.

## Carbon monoxide poisoning

Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia. There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK

Questions may hint at badly maintained housing e.g. student houses

Features of carbon monoxide toxicity

- headache: 90% of cases
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

Typical carboxyhaemoglobin levels

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting
- > 30% severe toxicity

Management

- 100% oxygen
- hyperbaric oxygen

Indications for hyperbaric oxygen\*

- loss of consciousness at any point
- neurological signs other than headache
- myocardial ischaemia or arrhythmia
- pregnancy

\*as stated in the 2008 Department of Health publication 'Recognising Carbon Monoxide Poisoning'

Question 1 of 18

A 62-year-old man is currently being treated with linezolid for MRSA bacteraemia. Which of the following medications may need to be discontinued whilst this is being administered?

[Metformin15% Citalopram39% Alendronic acid12% Candesartan9% Atorvastatin25%](#)

Linezolid was originally discovered as a psychotropic agent with antidepressant effects through mild reversible nonselective inhibition of monoamine oxidase (MAO), before it was found to have antibiotic efficacy against drug-resistant gram-positive cocci. In combination with serotonin agonists there is a risk of serotonin syndrome. Therefore, when using linezolid it must be considered to discontinue SSRIs.

There are no known listed interactions between alendronic acid, candesartan and atorvastatin.

Linezolid may potentially enhance the hypoglycaemic effect of metformin. Therefore careful capillary glucose monitoring should occur in a patient on both medications, but this is not necessarily a reason to discontinue the drug.

## **Serotonin syndrome**

### **Causes**

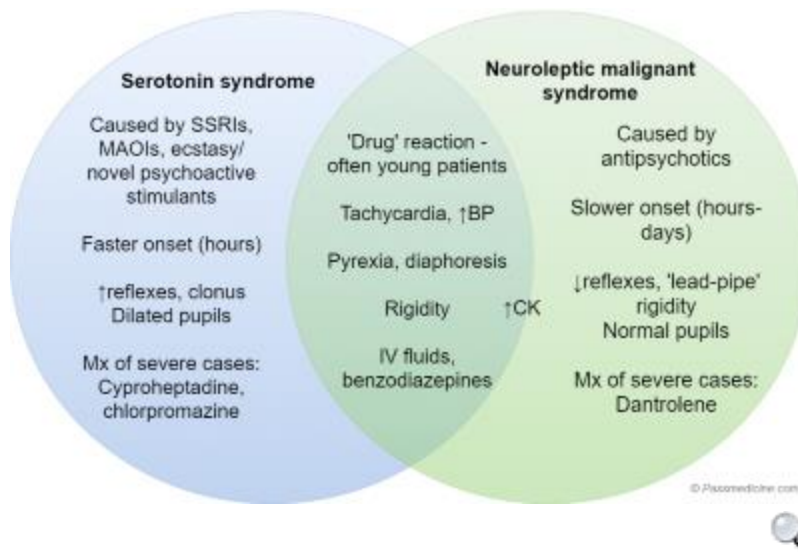
- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines

### **Features**

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state

## Management

- supportive including IV fluids
- benzodiazepines
- more severe cases are managed using serotonin antagonists such as cyproheptadine and chlorpromazine



Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

### Question 1 of 16

A 31 year old man is brought to the Emergency Department from a nightclub. He is accompanied by a friend who tells you he has taken the street drug NRG-1. The patient is agitated and difficult to assess as he will not stay on the trolley. He is sweating profusely and his skin has a blue tinge to it. Formal assessment is impossible but he is obviously confused and appears to be hallucinating. Examination shows a heart rate of 139bpm with a blood pressure of 158/105mmHg. Heart sounds are rapid but with no murmurs. The chest is clear to auscultation and oxygen saturations are 99% on air but his respiratory rate is 36/min. He is globally hypertonic with marked clonus in the lower limbs. Tympanic temperature is 40.6°C.

Blood results show:

Haemoglobin 129g/L	Sodium 119mmol/L	Creatine Kinase 1895ng/mL
Haematocrit 0.29	Potassium 5.5mmol/L	CRP 8.9mg/L

White cells 15.6x10<sup>9</sup>/L Chloride 90mmol/L  
Neutrophils 11.7x10<sup>9</sup>/L Urea 7.2mmol/L  
Platelets 303x10<sup>9</sup>/L Creatinine 100μmol/L

Urine is dilute but contains blood, protein and ketones on dipstick analysis

Which one of the following interventions is the most appropriate in the first instance?

[Rapid intravenous infusion of 0.9% sodium chloride with 1g IV paracetamol](#)19%[Rapid intravenous infusion of 3% sodium chloride with 1g IV paracetamol](#) 7%[Slow intravenous infusion of 3% sodium chloride with 10mg IV midazolam](#)24%[Slow intravenous infusion of 3% sodium chloride with 1g IV paracetamol and oral cyproheptadine 12mg](#)24%[Intravenous methylene blue \(methylthioninium chloride\) 1mg/kg over 5 minutes](#)26%

NRG-1, a synthetic cathinone, can cause agitation, hyponatraemia and serotonin syndrome. Treatment is with benzodiazepines, cooling and hypertonic saline if hyponatraemic. Patients may require intubation and paralysis to control hyperpyrexia. Hyperpyrexia is a consequence of muscle activity, not hypothalamic dysregulation so paracetamol is not useful. Indeed, if multiorgan failure develops, paracetamol is not conjugated and excreted safely, thus paracetamol toxicity may worsen the picture. Intravenous benzodiazepines are the mainstay in reducing agitation and helping to control muscle activity and this should be commenced in the short term. Given the concurrent hyponatraemia and elevated CK slow fluids with hypertonic saline is advised.

External cooling manoeuvres such as ice baths may be tried but when hyperpyrexia rises above 40°C it is safer to anaesthetise and paralyse patients and this patient is likely to warrant this.

Cyproheptadine is a specific 5HT-2A receptor antagonist and may be used in moderate serotonin syndrome. In this case, it is unlikely the patient will be cooperative enough to take it and its effects will be too slow. This option also includes paracetamol making this an incorrect answer.

Methylene blue is an antidote for methaemoglobinaemia; it would be unusual for NRG-1 to cause this although users of the drug often display a blue tinge to their skin for unknown reasons. The methaemoglobin level is not given here so use of methylene blue is not advisable.

## **Cathinone toxicity**

NRG-1 is a synthetic cathinone drug which is increasingly used recreationally.

Pharmacologically it is a derivative of phenylpropanone which is a naturally occurring psychotrope in khat (*Catha edulis*).

Synthetic cathinones became increasingly popular in the last ten years as an alternative to ecstasy since they were cheaper, easier to produce and initially were unrestricted. As legislation changes, chemical substitutions are made to molecular moieties to create similar drugs to avoid restrictions. All exert their effect by increasing synaptic concentrations of noradrenaline, dopamine and serotonin, giving users the sensation of euphoria, detachment and wellbeing as well as upregulation of the sympathetic system.

Toxicity is often seen due to lack of regulation of constituents and active ingredients. Tachycardia and hypertension may be seen due to the sympathomimetic effects of the drug and in some cases myocardial ischaemia can be seen. In the majority of cases of toxicity, however, similar to ecstasy toxicity, hyponatraemia and serotonin syndrome are seen. Hyponatraemia occurs as a consequence of significant water intake to reduce body temperature. Serum sodium levels may be markedly low and patients may present seizing.

If there is evidence of neurological compromise with an accompanying hyponatraemia, rapid correction of sodium is recommended with infusion of 3% saline solution at a maximum rate of 1ml/kg/hour. 0.9% saline solution is not recommended in patients with hyponatraemia and agitation due to the risk of worsening the hyponatraemia. Serotonin syndrome is due to massive flooding of synapses with liberated serotonin and causes agitation, confusion, muscle hyperactivity with fasciculations, hypertonia and clonus. Creatine kinase and white cell counts are often raised and body temperature may be extremely high.

#### Question 1 of 15

A 27 year old man is brought to the Emergency Department following a suspected deliberate overdose. On arrival he is drowsy with a GCS of 13/15 (E3V4M6) and confused. His airway is currently patent. The respiratory rate is 30 breaths per minute although oxygen saturations are 98% on 2L/min oxygen. The chest is clear to auscultation. Heart rate is 108bpm and blood pressure is 96/48mmHg. The ECG shows sinus tachycardia only. He complains of severe abdominal pain and is groaning on examination. There is significant tenderness in the right upper quadrant. Bowel sounds are hyperactive. Neurological examination is difficult but discloses downgoing plantars and reactive, mid-size pupils.

Blood tests show:

Haemoglobin	112g/L	Sodium	131mmol/L	Glucose	17.8mmol
MCV	96fL	Potassium	Haemolysed	Lactate	5.3mmol/L
White cells	15.7x10 <sup>9</sup> /L	Urea	15.6mmol/L	pH	7.14
Neutrophils	13.7x10 <sup>9</sup> /L	Creatinine	207mol/L	pCO <sub>2</sub>	2.9kPa
Platelets	278x10 <sup>9</sup> /L	ALP	234U/L	pO <sub>2</sub>	19.2kPa



INR	1.2	ALT	2453U/L	Bicarbonate 9.4mmol/L
PT	14secs	AST	3109U/L	Base excess -15.4mEq/L
APTT	49.2secs	Bilirubin	36mol/L	Anion gap 30.8

The laboratory comments there is significant haemolysis of the samples.

He has a massive vomit during assessment of black liquid and fresh blood.

Which of the following drugs is this patient most likely to have overdosed upon?

[Aspirin29% Ferrous sulphate36% Ibuprofen 9% Paracetamol18% Venlafaxine7%](#)

Severe iron toxicity presents with liver failure, gastrointestinal caustic damage and coagulopathy with raised APTT. Early hyperglycaemia and extensively haemolysed samples may also indicate significant iron burden

Iron is a surprisingly toxic drug. When taken in overdose symptoms may be expected to be seen at ingestions of 20mg/kg. 200mg/kg can be expected to be fatal. Symptoms of direct corrosion on the gastrointestinal tract may be seen within six hours of ingestion with abdominal pain, vomiting, diarrhoea and GI bleeding. Stool and vomitus may be black or grey unless frank bleeding predominates. During this interval, a hallmark of iron toxicity is a raised blood glucose; only few drugs may cause this in overdose. Hypoglycaemia occurs later in presentation due to liver failure. Other early features may include a neutrophil leucocytosis and significant haemolysis of samples due to the high plasma iron burden. Arterial blood gases will show a significant metabolic acidosis with a high anion gap. Lactate may be elevated but not sufficiently to explain the anion gap. Coagulopathy develops rapidly but the APTT tends to be prolonged in iron toxicity compared to the prolongation of prothrombin time in a paracetamol poisoning. In the ensuing hours, iron deposition within the myocardium, brain and liver can be expected to cause rapid cardiac failure, encephalopathy and hepatocellular necrosis with liver failure respectively. Renal failure develops due to hypovolaemia and acute tubular necrosis. Unless treated, death may result from haemorrhagic volume loss or from hepatic failure, although in significant overdose, early death results from respiratory failure due to coma. Treatment for iron overdose is with decontamination of the bowel, including whole bowel irrigation if needed and chelation therapy with desferrioxamine.

Although paracetamol toxicity can be expected to cause fulminant hepatic failure with renal failure and coagulopathy, the INR would be expected to be significantly deranged if this was the culpable drug given the extent of other organ damage. Also hypoglycaemia would be expected due to liver failure.

Aspirin when taken in significant overdose causes a characteristic constellation of symptoms including metabolic acidosis (although alkalosis may be seen at lower dose intoxications), convulsions, tinnitus, hyperpyrexia and pulmonary oedema. Often ventricular arrhythmia occurs due to metabolic acidosis and intracellular anaerobic respiration. Rarely coagulopathy develops but usually in association with disseminated intravascular coagulation which is not the case here. Aspirin overdoses may present with hyperglycaemia however and along with iron and aminophylline these agents should be considered when unexplained hyperglycaemia is seen.

Ibuprofen and other non steroidal are of low toxicity unless taken in massive overdose. Gastrointestinal upset and occasional GI haemorrhaging may be seen but liver failure and coagulopathy is rare. In massive overdose, central nervous depression with cerebellar signs and global electrolyte imbalances may be seen with blood dyscrasias. Multi-organ failure may develop but individual organ dysfunction is less likely.

Venlafaxine, a noradrenaline and serotonin modulator, may cause serotonin syndrome and sympathomimetic symptoms, including arrhythmia, hyperpyrexia and respiratory failure. Hepatitis is rare.

## Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Management	Treatment
<b>Paracetamol</b>	<ul style="list-style-type: none"> <li>activated charcoal if ingested &lt; 1 hour ago</li> <li>N-acetylcysteine (NAC)</li> <li>liver transplantation</li> </ul>	
<b>Salicylate</b>	<p>Management</p> <ul style="list-style-type: none"> <li>urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning</li> <li>haemodialysis</li> </ul>	
<b>Opioid/opiates</b>	Naloxone	
<b>Benzodiazepines</b>	Flumazenil	
<b>Tricyclic antidepressants</b>	<p>Management</p> <ul style="list-style-type: none"> <li>IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity</li> <li>arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias</li> </ul>	

<b>Toxin</b>	<b>Treatment</b>
	<ul style="list-style-type: none"> <li>dialysis is ineffective in removing tricyclics</li> </ul>
	Management
<b>Lithium</b>	<ul style="list-style-type: none"> <li>mild-moderate toxicity may respond to volume resuscitation with normal saline</li> <li>haemodialysis may be needed in severe toxicity</li> <li>sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion</li> </ul>
<b>Warfarin</b>	Vitamin K, prothrombin complex
<b>Heparin</b>	Protamine sulphate
	Management
<b>Beta-blockers</b>	<ul style="list-style-type: none"> <li>if bradycardic then atropine</li> <li>in resistant cases glucagon may be used</li> </ul>
	Management has changed in recent times
<b>Ethylene glycol</b>	<ul style="list-style-type: none"> <li>ethanol has been used for many years</li> <li>works by competing with ethylene glycol for the enzyme alcohol dehydrogenase</li> <li>this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning</li> <li><b>fomepizole</b>, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol</li> <li>haemodialysis also has a role in refractory cases</li> </ul>
	Management
<b>Methanol poisoning</b>	<ul style="list-style-type: none"> <li>fomepizole or ethanol</li> <li>haemodialysis</li> </ul>
	Management
<b>Organophosphate insecticides</b>	<ul style="list-style-type: none"> <li>atropine</li> <li>the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit</li> </ul>
<b>Digoxin</b>	Digoxin-specific antibody fragments
<b>Iron</b>	Desferrioxamine, a chelating agent

Toxin	Treatment
Lead	Dimercaprol, calcium edetate Management
Carbon monoxide	<ul style="list-style-type: none"> <li>100% oxygen</li> <li>hyperbaric oxygen</li> </ul>
Cyanide	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate

#### Question 2 of 15

A 21-year-old woman presents to the emergency department after her flatmate found her drowsy in her bedroom. She had been incontinent of urine.

On examination the patient is obtunded with a Glasgow Coma Score of 7 (E1V2M4). The pupils are 7mm bilaterally and sluggishly reactive to light. The heart rate is 133bpm and the blood pressure is 99/65mmHg.

A 12-lead ECG reveals sinus tachycardia with a QT interval of 510ms. The QRS duration is 115ms.

What is the most likely cause for this patient's presentation?

[Amyl nitrate toxicity](#)7%[Gamma hydroxybutyric acid toxicity](#)9%[Toluene solvent toxicity](#)7%[Tricyclic antidepressant toxicity](#)71%[Heroin toxicity](#)6%

Dilated pupils in combination with ECG changes including prolonged QT interval and QRS duration (borderline prolonged in this case) should suggest tricyclic antidepressant toxicity.

Features of toluene toxicity include irritation to the eyes, nose and respiratory tract from inhalation, along with confusion, ataxia, headache, slurred speech and euphoria. Prolongation of the QT interval is not usually associated.

Features of amyl nitrate toxicity include blurred vision, xanthopsia and haemoptysis. It does not typically affect the corrected QT interval.

Features of gamma hydroxybutyric acid (GHB) toxicity include CNS and respiratory depression, hypersalivation, bradycardia and hypotension. It does not typically affect the corrected QT interval.

Heroin toxicity typically results in depression of the respiratory and central nervous systems and pin-point pupils (rather than mydriasis in this case). It does not typically affect the corrected QT

interval.

([www.toxbase.org](http://www.toxbase.org))

## **Tricyclic overdose**

Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and doxepin (dothiepin) are particularly dangerous in overdose.

Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- arrhythmias
- seizures
- metabolic acidosis
- coma

ECG changes include:

- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

## **Management**

- IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics

### Question 3 of 15

An 82-year-old man presents with pain following a fall. He was brought in by ambulance after he slipped and hurt himself on the pavement. He ended up tripping whilst returning from the local shops. He remembers his fall and noted immediate pain in his right leg, and was unable to get up. A passerby called an ambulance and he was brought into the hospital. He has a past medical history of ischaemic heart disease, mild dementia, hypertension and high cholesterol.

Pelvic X-rays demonstrated an intertrochanteric right hip fracture. He is due to be operated on within the five hours and is put nil by mouth and started on IV fluids. How should his risk of venous thromboembolism (VTE) be managed?

[Low molecular weight heparin before surgery](#)21%[Unfractionated heparin before surgery](#)14%[Delay VTE prophylaxis until following surgery](#)19%[Mechanical VTE prophylaxis before surgery](#)35%[IV heparin infusion until surgery](#)10%

The correct answer is mechanical VTE prophylaxis before surgery. This is a patient with a hip fracture due to be operated on within 12 hours. He should have careful mechanical VTE prophylaxis with stockings or pneumatic compression despite having a fracture. If surgery was to occur in over 12 hours then low molecular weight heparin should be started, with the last dose given 12 hours before surgery. If he also had renal failure, then unfractionated heparin should be used and also stopped 12 hours before surgery.

Source:

'Venous thromboembolism: reducing the risk for patients in hospital' Clinical guideline [CG92]. The National Institute for Health and Care Excellence, January 2010.

## Heparin

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	Standard heparin	Low molecular weight heparin (LMWH)
<b>Administration</b>	Intravenous	Subcutaneous
<b>Duration of</b>	Short	Long

	<b>Standard heparin</b>	<b>Low molecular weight heparin (LMWH)</b>
<b>action</b>		
<b>Mechanism of action</b>	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, Xia and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
<b>Side-effects</b>	Bleeding Heparin-induced thrombocytopenia (HIT) Osteoporosis	Bleeding Lower risk of HIT and osteoporosis with LMWH
<b>Monitoring</b>	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
<b>Notes</b>	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

#### Heparin-induced thrombocytopenia (HIT)

- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

#### Question 4 of 15

A 55-year-old man is brought to the Emergency department after a house fire. According to ambulance crews, he was initially agitated and confused with tachycardia and hypertension, coupled with vomiting at the scene, but has become progressively more drowsy and confused. On arrival his blood pressure is 85/60 mmHg, his pulse is 38 beats per minute, respiratory rate is 10 breaths per minute and there are inspiratory crackles throughout on auscultation. His skin is flushed, you note incomprehensible moaning on abdominal palpation. Oxygen and IV fluids are

commenced. Venous blood gas reveals a metabolic acidosis with a marked elevation in serum lactate.

Which of the following is the most appropriate intervention?

[Amyl nitrate 22% Atropine 20% Dicobalt edetate 34% DMSA 18% Vitamin C 5%](#)

Intravenous dicobalt edetate is the UK recommended IV therapy for life-threatening cyanide overdose, the most likely diagnosis here after exposure in a house fire. It is associated with significant metabolic acidosis with a marked elevation in serum lactate and left untreated can be fatal. Timely intervention is essential. Hydroxycobalamin may also be used in the acute setting.

Amyl nitrate is an inhaled antidote for cyanide poisoning and can be considered where IV access can't be rapidly obtained. Alpha / beta adrenergic agonists rather than anticholinergics may be considered as an additional intervention. DMSA is used as a treatment for lead toxicity, and vitamin C is used in the treatment of methaemoglobinemia.

## **Cyanide poisoning**

Cyanide may be used in insecticides, photograph development and the production of certain metals. Toxicity results from reversible inhibition of cellular oxidising enzymes

### **Presentation**

- 'classical' features: brick-red skin, smell of bitter almonds
- acute: hypoxia, hypotension, headache, confusion
- chronic: ataxia, peripheral neuropathy, dermatitis

### **Management**

- supportive measures: 100% oxygen
- definitive: hydroxocobalamin (intravenously), also combination of amyl nitrite (inhaled), sodium nitrite (intravenously), and sodium thiosulfate (intravenously)



A 57-year-old male is admitted to hospital with an acute kidney injury (AKI). His past medical history includes polycystic kidney disease for which he received a renal transplant 4 years ago, and type 2 diabetes mellitus. His drug history includes tacrolimus, mycophenolate mofetil, amlodipine and simvastatin. Tacrolimus toxicity is suspected to have caused his AKI.

He informs you that he has only recently been discharged, where he was started on rifampicin and erythromycin for Legionnaires' disease. He was also started on pioglitazone after a diabetic team review.

Which of his other medications is the most likely culprit of the tacrolimus toxicity?

[Pioglitazone5%Erythromycin57%Simvastatin6%Rifampicin27%Mycophenolate mofetil5%](#)

Despite his complicated medical and drug history, this is a relatively simple question about drug interactions.

Erythromycin is a potent inhibitor of the cytochrome P450 system, which means it can have a rapid effect on levels of other drugs metabolised by this system, e.g. tacrolimus, warfarin.

Clarithromycin, fluconazole and clotrimazole are also inhibitors.

Rifampicin is an enzyme inducer, which would cause decreased tacrolimus concentrations, potentially leading to symptoms of organ rejection.

## **P450 enzyme system**

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inducers of the P450 system include

- antiepileptics: phenytoin, carbamazepine
- barbiturates: phenobarbitone
- rifampicin
- St John's Wort
- chronic alcohol intake
- griseofulvin
- smoking (affects CYP1A2, reason why smokers require more aminophylline)

Inhibitors of the P450 system include

- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- cimetidine, omeprazole
- amiodarone
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- ritonavir
- sodium valproate
- acute alcohol intake
- quinupristin

#### Question 2 of 10

A 30-year-old man was referred to endocrinology clinic for the assessment of the adverse consequences of anabolic steroid use. The patient reported that he had recently decided to stop using anabolic steroids, having been a regular user for the previous 5 years to support his body-building training. The patient cited the potential health risks of long-term anabolic steroid use as the reason behind his decision to cease his use.

The patient had followed a regime of an intramuscular injection of long-acting synthetic testosterone derivative every two weeks. The patient took a 4-week break from anabolic steroids every 12 weeks, in an attempt to limit the adverse side-effects. The patient denied ever having used oral or topical synthetic testosterone preparations and had always used sterile injecting equipment.

The patient stated that he had developed significant gynaecomastia and also suffered significant male pattern baldness since starting to use anabolic steroids. In addition, 2 years previously he had suffered a ruptured right biceps tendon while exercising, requiring a surgical repair and had a prolonged period of rehabilitation. There was no history of symptoms suggestive of cardiac or liver disease. The patient took no regular prescribed medications and reported an alcohol consumption of between 15 to 20 units per week.

General examination of the patient revealed a highly muscular and lean adult male. Moderate gynaecomastia was present, but there were no other signs of chronic liver disease. Examination of the cardiovascular and respiratory systems was unremarkable.

Please see below for the available results of blood tests taken prior to the patient's attendance at the clinic.

HbA1C	47 mmol / mol (reference < 42)
Total cholesterol	6.1 mmol / L (reference < 5.0)

Fasting LDL cholesterol	5.0 mmol / L (reference < 3.0)
Fasting HDL cholesterol	1.1 mmol / L (reference > 1.2)
Prolactin	490 mU / L (reference 80 - 400)
Luteinising hormone	<i>result pending</i>
Follicle-stimulating hormone	<i>result pending</i>
Testosterone	<i>result pending</i>
Epitestosterone	<i>result pending</i>

What pattern of results for the pending blood tests is consistent with the patient's anabolic steroid use?

[Elevated testosterone:epitestosterone ratio; normal luteinising hormone; normal follicle-stimulating hormone7%Suppressed testosterone:epitestosterone ratio; elevated luteinising hormone; suppressed follicle-stimulating hormone18%Suppressed testosterone:epitestosterone ratio; suppressed luteinising hormone; suppressed follicle-stimulating hormone21%Elevated testosterone:epitestosterone ratio; suppressed luteinising hormone; suppressed follicle-stimulating hormone47%Normal testosterone:epitestosterone ratio; elevated luteinising hormone; elevated follicle-stimulating hormone7%](#)

The patient has developed some of the typical unwanted effects associated with anabolic steroid use; namely gynaecomastia and accelerated male pattern baldness. In addition, tendon rupture is frequently associated with anabolic steroid use due to the disproportionate enhancement of muscle bulk compared to tendon strength. Other common unwanted effects include acne, testicular atrophy (or clitoral hypertrophy in females), impaired glucose tolerance and a deranged blood lipid profile. More worryingly, anabolic steroid use is also associated with serious liver disease and an increased mortality from heart disease.

Epitestosterone is a naturally occurring stereoisomer of testosterone produced by the testes. In healthy males, the testosterone:epitestosterone ratio is typically 1:1. However, exogenous administration of testosterone does not increase levels of epitestosterone, so anabolic steroid use is associated with an increase in the testosterone:epitestosterone ratio (typically to greater than 4:1). In anti-doping testing for competitive sports, an elevated testosterone:epitestosterone ratio is considered possible evidence of anabolic steroid use.

Physiological production of testosterone is promoted by the release of the gonadotropins luteinising hormone and follicle stimulating hormone by the pituitary gland. Both these hormones increase the number of testosterone-producing Leydig cells in the testes, with luteinising hormone also increasing testosterone production by Leydig cells. Elevated testosterone levels reduce gonadotropin production via negative feedback to the hypothalamus (causing reduced gonadotropin releasing hormone production) and the pituitary gland. Therefore, high levels of exogenous testosterone will act to suppress luteinising hormone and follicle stimulating hormone.

Brooks J, Ahmad I, Easton G. Anabolic steroid use. BMJ 2016;353:i5023.

## Anabolic steroid use

Anabolic steroid use is associated with several serious long-term health consequences. Cardiac morbidity and mortality are increased by anabolic steroid use, although the precise mechanism of this effect is unclear. Hepatic side effects also occur secondary to chronic vascular injury: these include hepatocellular carcinoma and hepatic adenoma. Psychiatric illness is also commonly co-morbid with anabolic steroid use. Additionally, users who inject anabolic steroids have an increased risk of blood-borne viruses if needles are shared between individuals.

Due to the above concerns, patients should be strongly counselled to stop using anabolic steroids. There is no requirement for tapering of doses. Many of the above blood test abnormalities normalise once anabolic steroid consumption ceases. The expert recommendation is for lifelong monitoring for potential complications, initially annually with frequency reducing once blood markers normalise and in the absence of apparent adverse effects.

Brooks J, Ahmad I, Easton G. Anabolic steroid use. *BMJ* 2016;353:i5023.

### Question 3 of 10

A 59- year- old male presented with palpitations, excessive sweating and weight loss for two months. Two years ago he was diagnosed with atrial fibrillation and commenced on amiodarone.

On examination, his pulse rate is 80 beats per minute, irregularly irregular, and his blood pressure is 135/80. There was no goitre, no eye signs or hand signs.

Investigations reveal:

Serum free T4	60 pmol/l
Serum free T3	15 pmol/l (5-10)
Serum TSH	<0.05 mU/l
Serum antithyroid peroxidase	negative
TSH receptor antibodies	negative

Radioactive iodine uptake scan showed reduced uptake by the thyroid gland.

What is the most appropriate management for this patient?

[Discontinue amiodarone and give carbimazole19%](#)[Discontinue amiodarone and give potassium perchlorate8%](#)[Discontinue amiodarone and give prednisolone65%](#)[Radioactive iodine4%](#)[Total thyroidectomy4%](#)

The diagnosis is amiodarone induced thyrotoxicosis (AIT) type 2 which is a destructive thyroiditis treated with prednisolone.

AIT type 2 is differentiated from AIT type 1 by the reduced iodine uptake, absence of thyroid autoantibodies and absence of goitre.

AIT type 1 is treated with carbimazole or potassium perchlorate.

If amiodarone could not be stopped as in ventricular tachycardia, then total thyroidectomy should be considered.

## **Amiodarone and the thyroid gland**

Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

### **Amiodarone-induced hypothyroidism**

The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect\*

Amiodarone may be continued if this is desirable

### **Amiodarone-induced thyrotoxicosis**

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

	<b>AIT type 1</b>	<b>AIT type 2</b>
Pathophysiology	Excess iodine-induced thyroid hormone synthesis	Amiodarone-related destructive thyroiditis
Goitre	Present	Absent
Management	Carbimazole or potassium perchlorate	Corticosteroids

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT

\*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

Question 4 of 10

A 23-year-old male is brought to the ED via ambulance after a seizure. His friends reported an episode of jerking of all four limbs lasting 1-2 minutes associated with urinary incontinence.

He has vomited twice in the ED and is complaining of muscle aches.

On examination the patient is agitated, confused and appears to be hallucinating. Myoclonic jerks are present. The chest is clear to auscultation and oxygen saturations are 98% on room air. Heart sounds are normal, the pulse rate is 130bpm and the blood pressure is 161/84mmHg.

An ECG reveals sinus tachycardia. The pupils measure 8mm and are equal and reactive. The patient's temperature is 36.6°C.

Blood tests reveal:

Hb	138 g/l
Platelets	$362 \times 10^9/l$
WBC	$11.2 \times 10^9/l$
Na <sup>+</sup>	135 mmol/l
K <sup>+</sup>	2.7 mmol/l
Urea	12.6 mmol/l
Creatinine	187 µmol/l
Bilirubin	18 µmol/l
ALP	98 u/l
ALT	53 u/l
γGT	27 u/l
Albumin	32 g/l

What is the most likely cause for this patient's presentation?

[Toluene solvent toxicity13%](#)[Amyl nitrate toxicity17%](#)[Gamma hydroxybutyric acid toxicity26%](#)[Synthetic cannabinoid toxicity34%](#)[Heroin toxicity10%](#)

The hallucinations, seizure, myoclonus, mydriasis, hypertension, acute kidney injury and hypokalaemia are consistent with synthetic cannabinoid toxicity.

Features of toluene toxicity can be similar however irritation to the eyes, nose and respiratory

tract is often seen from inhalation in toluene abuse.

Amyl nitrate is a vasodilator so toxicity tends to result in hypotension rather than hypertension as in this case. Other features of amyl nitrate toxicity include blurred vision, xanthopsia and haemoptysis.

Features of gamma hydroxybutyric acid (GHB) toxicity include CNS and respiratory depression, hypersalivation, bradycardia and hypotension.

Heroin toxicity typically results in depression of the respiratory and central nervous systems and pin-point pupils (rather than mydriasis in this case).

([www.toxbase.org](http://www.toxbase.org))

## **Cannabis**

Features of synthetic cannabinoid toxicity include:

CNS: agitation, tremor, anxiety, confusion, somnolence, syncope, hallucinations, changes in perception, acute psychosis, nystagmus, convulsions and coma.

Cardiac: tachycardia, hypertension, chest pain, palpitations, ECG changes.

Renal: acute kidney injury.

Muscular: hypertonia, myoclonus, muscle jerking and myalgia.

Other: cold extremities, dry mouth, dyspnoea, mydriasis, vomiting and hypokalaemia

### **Question 5 of 10**

A 37-year-old man attends endocrinology clinic for assessment of the unwanted effects of long-term anabolic steroid use. The patient had been a competitive bodybuilder, who had used anabolic steroids to enhance his training regime, but now stated that he had 'retired' from bodybuilding last week and so stopped using steroids. The patient was concerned about the long-term health consequences of his previous use.

The patient described a 10-year period of anabolic steroid use. Typically he would take a daily

oral formulation of a synthetic testosterone supplemented by an intramuscular injection of a longer acting agent every few weeks. The patient would take breaks from anabolic steroid use intermittently throughout the year, to reduce unwanted effects and also to evade anti-doping testing arranged by the organisers of the competitions in which he competed. The patient stated that he had never shared or reused needles when injecting himself with anabolic steroids.

The patient reported a range of unwanted effects he had developed secondary to his anabolic steroid use. These included severe acne affecting the patient's face and chest, intermittent symptoms of gastrointestinal dysfunction, and male pattern baldness. When asked directly, the patient reported that he had suffered from erectile dysfunction and scrotal discomfort towards the end of his use of anabolic steroids. The patient did not report any other concerns, in particular, he denied symptoms associated with heart or liver disease. The patient had no other significant past medical history and disclosed being a former user of recreational drugs, including cocaine.

Examination of the patient's cardiovascular and respiratory symptoms was unremarkable except for moderate pitting oedema to the level of the mid-tibia bilaterally. Examination of the abdomen noted mild bilateral gynaecomastia but no other signs of chronic liver disease. The patient's testicular volume was estimated as 18 ml bilaterally. A brief mental state examination did not reveal any evidence of a significant mood or anxiety disorder.

HbA1C	47 mmol / mol (reference < 42)
Fasting LDL cholesterol	4.5 mmol / L (reference < 3.0)
Fasting HDL cholesterol	1.0 mmol / L (reference > 1.2)
Prolactin	501 mU / L (reference 80 - 400)
Luteinising hormone	1.4 IU / L (reference 1.8 - 8.6)
Follicle-stimulating hormone	1.2 mU / ml (reference 1.5 - 12.4)
Transthoracic echocardiogram	Normal systolic and diastolic function; no left ventricular hypertrophy; normal valvular function

Which of the patient's unwanted effects will be irreversible with cessation of steroid use?

[Pitting oedema8%Erectile dysfunction16%Scrotal pain6%Male pattern baldness64%Gastrointestinal dysfunction7%](#)

Anabolic steroid use is associated with a wide variety of unwanted effects. Morbidity and mortality from cardiac diseases are increased, although the precise mechanism of this effect is unknown. In addition, serious liver disease - for example, hepatocellular carcinoma - is also associated with anabolic steroid use. There are a variety of less dangerous but troubling unwanted effects as described below, some of which will be irreversible with cessation of anabolic steroid use. Due to the potential risk to long-term health, anabolic steroid users should be strongly advised to stop their use. No tapering of the dose is required. Active or former users should be monitored lifelong for evidence of complications.

Reversible unwanted effects of anabolic steroids include:



- Increased appetite
- Gastrointestinal dysfunction
- Mood swings
- Anxiety
- Acne
- Oedema
- Libido change
- Scrotal pain
- Erectile dysfunction
- Menstrual irregularities

Irreversible unwanted effects of anabolic steroids include:

- Hirsutism
- Voice pitch changes
- Male pattern baldness
- Skin striae or keloid scarring
- Chest pain
- Clitoral hypertrophy
- Short stature due to premature fusion of growth plates

It is unclear whether other unwanted effects are reversible with cessation of anabolic steroids; for example, gynaecomastia, testicular atrophy and infertility. Some limited studies suggest that normal sperm production and fertility return following cessation of anabolic steroid use, although on a timescale ranging from 4 months to 5 years.

The patient also has a typical pattern of hormonal irregularities associated with anabolic steroid use. A deranged lipid profile and impaired glucose tolerance are also frequently observed. The patient's echocardiogram is reassuringly normal, which suggests that his leg oedema will resolve with cessation of anabolic steroid use.

Brooks J, Ahmad I, Easton G. Anabolic steroid use. BMJ 2016;353:i5023.

## **Anabolic steroid use**

Anabolic steroid use is associated with several serious long-term health consequences. Cardiac morbidity and mortality are increased by anabolic steroid use, although the precise mechanism of this effect is unclear. Hepatic side effects also occur secondary to chronic vascular injury: these include hepatocellular carcinoma and hepatic adenoma. Psychiatric illness is also commonly comorbid with anabolic steroid use. Additionally, users who inject anabolic steroids have an

increased risk of blood-borne viruses if needles are shared between individuals.

Due to the above concerns, patients should be strongly counselled to stop using anabolic steroids. There is no requirement for tapering of doses. Many of the above blood test abnormalities normalise once anabolic steroid consumption ceases. The expert recommendation is for lifelong monitoring for potential complications, initially annually with frequency reducing once blood markers normalise and in the absence of apparent adverse effects.

Brooks J, Ahmad I, Easton G. Anabolic steroid use. BMJ 2016;353:i5023.

#### Question 6 of 10

A 46-year-old male was transferred to the Intensive Care Unit (ICU) as an emergency admission. He had been scheduled to undergo an elective open cholecystectomy under general anaesthetic. He had been intubated and ventilated successfully, but a few minutes into the operation he had become tachycardic, with his heart rate rising from a resting rate of 72 bpm to a rate of 142bpm. His oxygen saturations dropped down to 92% on 15 litres of oxygen per minute, and his blood pressure rose from his baseline of 114/78 mmHg up to 162/98 mmHg. In addition, his end tidal CO<sub>2</sub> concentration rose, despite several checks to ensure that the tracheal tube was correctly sited. His past medical history was unremarkable except for an appendicectomy under general anaesthetic aged 26 yrs old.

The operation was abandoned. Upon his arrival to ICU, he was intubated and ventilated, maintaining an oxygen saturation of 96% on 15 litres per minute of oxygen. He appeared flushed and had significant muscle rigidity. His blood pressure had risen to 174/102 mmHg, and his heart rate was 136bpm. His temperature was 38.2 C. Examination of the cardiovascular revealed vasodilated peripheries with a bounding pulse and normal heart sounds. Auscultation of the lungs revealed good air entry in all zones and a correctly cited tracheal tube. Examination of the abdomen was unremarkable. Examination of the neurological system confirmed the presence of equal and reactive pupils, with generalised muscle hypertonicity and masseter muscle spasm. A central venous catheter and arterial line were inserted. The central venous pressure was 9 cm.

An arterial blood gas sample on 15 litres of oxygen was taken:

pH 7.26  
HCO<sub>3</sub> 18 mmol/l  
PaO<sub>2</sub> 17 kPa  
PaCO<sub>2</sub> 7.6 kPa  
Na<sup>+</sup> 139 mmol/l  
K<sup>+</sup> 7.1 mmol/l

What is the next best immediate management step?

[Commence IV labetalol infusion7%](#)[Commence IV meropenem6%](#)[Commence high dose IV hydrocortisone10%](#)[Commence IV dantrolene66%](#)[Arrange immediate therapeutic hypothermia10%](#)

This patient has developed malignant hyperthermia as a result of his anaesthetic. In addition to stopping the responsible anaesthetic agent, the best immediate management step involves commencing IV dantrolene. Early commencement of dantrolene has greatly reduced mortality associated with malignant hyperthermia and should be administered as soon as the diagnosis is suspected. Note that hyperthermia is a relatively late feature of malignant hyperthermia, and earlier features include hypoxia, hypercarbia, masseter muscle spasm and hypertonicity.

## **Malignant hyperthermia**

### Overview

- condition often seen following administration of anaesthetic agents
- characterised by hyperpyrexia and muscle rigidity
- cause by excessive release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum of skeletal muscle
- associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

### Causative agents

- halothane
- suxamethonium
- other drugs: antipsychotics (neuroleptic malignant syndrome)

### Investigations

- CK raised
- contracture tests with halothane and caffeine

### Management

- dantrolene - prevents  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum

#### Question 7 of 10

A 24-year-old man presents to the accident and emergency department with his girlfriend after collapsing in a nightclub at 0400hrs. It is now 0600hrs. On examination he is V on the AVPU scale with dry mucous membranes, he has flushed skin and feels very warm to the touch. There is mildly increased muscle tone, myoclonic jerks and hyperreflexia globally but worse in the lower limbs. Pupils are dilated but respond to light equally and bilaterally. He is disorientated and agitated during the examination, thrashing about in the bed and occasionally lashing out at people.

Heart rate 126/min, blood pressure 90/60 mmHg, respiratory rate 18/min, temperature =  $40.3^{\circ}\text{C}$ , sats 97% on 10l of oxygen.

$\text{Na}^{+}$	136 mmol/l
$\text{K}^{+}$	3.9 mmol/l
Urea	2.3 mmol/l
Creatinine	77 $\mu\text{mol/l}$
Glucose	4.6 mmol/l
Creatinine kinase	12,000 U/l

Bilirubin	25 $\mu\text{mol/l}$
ALP	185 u/l
ALT	125 u/l
$\gamma\text{GT}$	144 u/l
Albumin	40 g/l

CT Head: No abnormality detected.

Lumbar puncture reveals:

Opening pressure	15 cmCSF
Appearance	Clear
Glucose	3.5 mmol/l
Protein	0.3 g/l
White cells	4 / $\text{mm}^3$

He has a past medical history of schizoaffective disorder. His girlfriend shows you his regular medications, the prescription has been unchanged for 1 year. Olanzapine 15mg and Sertraline 150mg. His girlfriend tells you that he took an unknown white powder whilst in the club

What is the most appropriate treatment plan?

[IV Ceftriaxone5%Stop Olanzapine and give dantrolene32%Stop sertraline and give IV lorazepam and consider cyproheptadine39%Give IV naloxone6%Stop olanzapine and sertraline and supportive therapy18%](#)

The diagnosis is MDMA intoxication which has led to serotonin syndrome and rhabdomyolysis. The treatment for serotonin syndrome is stopping any serotonergic agents, using benzodiazepines for agitation and consideration of the use of serotonin antagonists such as cyproheptadine if there is severe autonomic disturbance. MDMA intoxication can lead to serotonin syndrome, especially if used in conjunction with any drug which increased serotonin transport across the synapses eg SSRIs such as sertraline.

Serotonin syndrome presents with agitation, reduced consciousness, flushing of the skin, hyperthermia, hyperreflexia, myoclonus (worse in the lower limbs), tachycardia, hypertension or labile BP. Most cases of serotonin syndrome present within 6 hours of any change in medication or dose i.e in this case after the MDMA.

Neuroleptic malignant syndrome would present in a similar way and would be treated by option B. However NMS usually evolves over 1-3 days with extreme muscle rigidity being a characteristic feature. NMS is less likely when on a lower potency antipsychotic such as Olanzapine and less likely when the dose has been stable for a long period of time.

Heroin overdose would not present with these features. Dilated pupils essentially rule this out and heroin is not usually a white powder which makes option D less likely.

Although meningitis can present with fever and reduced consciousness the normal LP rules out this diagnosis and therefore option A is an inappropriate treatment

Option E is inappropriate as this gentleman is severely unwell with autonomic instability, severe hyperthermia and significant rhabdomyolysis with renal impairment. Active management other than supportive treatment would be recommended for this individual if the diagnosis were NMS or serotonin syndrome

**Ecstasy poisoning**

Ecstasy (MDMA, 3,4-Methylenedioxymethamphetamine) use became popular in the 1990's during the emergence of dance music culture

#### Clinical features

- neurological: agitation, anxiety, confusion, ataxia
- cardiovascular: tachycardia, hypertension
- hyponatraemia
- hyperthermia
- rhabdomyolysis

#### Management

- supportive
- dantrolene may be used for hyperthermia if simple measures fail

#### Question 1 of 2

A 61 year old man with a history of bipolar affective disorder presents to the Emergency Department with a 2 week history of feeling unwell. This started off as a coarse tremor in the limbs and has now progressed to slurred speech and disorientation. On examination you find an ataxic gait and myoclonus. His lithium level 2.6. You diagnose lithium toxicity. In addition to bipolar affective disorder, he has a history of rheumatoid arthritis, atrial fibrillation and GORD. Which of the following recent events is most likely to explain the cause of his toxicity?

[Recent addition of carbamazepine to augment lithium17%](#) [Recent prescription of naproxen for knee pain47%](#) [Recent increase in caffeine intake5%](#) [Recent addition of amiodarone for atrial fibrillation22%](#) [Recent use of sodium bicarbonate tablets for symptoms of dyspepsia8%](#)

The answer is B. NSAIDs reduce excretion of lithium in the kidneys and can therefore increase serum lithium levels and give rise to lithium toxicity as seen above. ACE inhibitors, ARBs and thiazide diuretics also reduce the kidneys ability to excrete lithium.

Caffeine and sodium bicarbonate both increase the excretion of lithium from the body and therefore will reduce serum lithium levels

When carbamazepine is added to lithium therapy, it is known to increase the risk of neurotoxicity, but it does this without increasing serum lithium levels. Similarly, use of amiodarone with lithium is known to increase the risk of VT, but it does this without increasing lithium levels

## **Lithium toxicity**

Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys. Lithium toxicity generally occurs following concentrations  $> 1.5$  mmol/L.

Toxicity may be precipitated by dehydration, renal failure, diuretics (especially bendroflumethiazide), ACE inhibitors, NSAIDs and metronidazole.

### Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- seizure
- coma

### Management

- mild-moderate toxicity may respond to volume resuscitation with normal saline
- haemodialysis may be needed in severe toxicity
- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion

Question 1 of 135

A 19-year-old man develops multiple tear-drop papules on his trunk and limbs. He is otherwise well. A diagnosis of guttate psoriasis is suspected. What is the most appropriate management?

[Oral penicillin for 14 days4% Reassurance + topical treatment if lesions are symptomatic64% Oral penicillin for 14 days + topical treatment if lesions are symptomatic15% Referral to secondary care6% Oral corticosteroids11%](#)

The British Association of Dermatologists state in their psoriasis guidelines that 'evidence does not support a therapeutic benefit from antibiotic therapy'.

**Psoriasis: guttate**

Guttate psoriasis is more common in children and adolescents. It may be precipitated by a streptococcal infection 2-4 weeks prior to the lesions appearing

Features

- tear drop papules on the trunk and limbs





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## Management

- most cases resolve spontaneously within 2-3 months
- there is no firm evidence to support the use of antibiotics to eradicate streptococcal infection
- topical agents as per psoriasis
- UVB phototherapy
- tonsillectomy may be necessary with recurrent episodes

## Differentiating guttate psoriasis and pityriasis rosea

	<b>Guttate psoriasis</b>	<b>Pityriasis rosea</b>
<b>Prodrome</b>	Classically preceded by a streptococcal sore throat 2-4 weeks	Many patients report recent respiratory tract infections but this is not common in questions
<b>Appearance</b>	'Tear drop', scaly papules on the trunk and limbs	Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions.  May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
<b>Treatment / natural history</b>	Most cases resolve spontaneously within 2-3 months Topical agents as per	Self-limiting, resolves after around 6 weeks

## **Guttate psoriasis**

psoriasis  
UVB phototherapy

## **Pityriasis rosea**

### Question 2 of 135

A 30-year-old lady was admitted with a painful ulcer on her right lower limb. At first, the patient described developing a painful erythematous area which then rapidly broke down to form a painful ulcer. The edges of the ulcer had a purple discolouration. She did recall recently knocking this area whilst riding her bike to work. She had recently been considering seeing her GP as she had been opening her bowels around eight times a day with some mucus and she had noticed some mild abdominal pain. She attributed this to irritable bowel syndrome which she is believed to have had since the age of 20 years.

Her past medical history included migraines and a right deep vein thrombosis after a flight to America. Her father had a family history of diabetes. She had a biopsy of the ulcer which showed heavy neutrophil infiltration.

What is the most likely diagnosis?

[Pyoderma gangrenosum 78%](#)[Erythema nodosum 6%](#)[Necrobiosis lipoidica 9%](#)[Leishmaniasis 3%](#)[Venous ulcer 5%](#)

This patient has Pyoderma gangrenosum with underlying undiagnosed inflammatory bowel disease.

Pyoderma gangrenosum is a rare, non-infectious, inflammatory disorder. It is an uncommon cause of very painful skin ulceration. It may affect any part of the skin, but the lower legs are the most common site. In 50% there is no underlying cause but in 10-15% it is associated with ulcerative colitis or Crohn's disease. Other associations include rheumatoid arthritis, myeloproliferative disorders, malignancy, and Wegener's granulomatosis.

Pyoderma gangrenosum is classified as a neutrophilic dermatosis. Neutrophilic dermatoses are skin conditions characterised by dense infiltration of neutrophils in the affected tissue and this is often seen on biopsy.

Pyoderma gangrenosum usually starts quite suddenly, often at the site of a minor injury as in this patient's case and this is known as pathergy. It may start as a small pustule, red bump or blood-blister. The skin then breaks down resulting in an ulcer which is often painful. The edge of the ulcer is often described as purple, violaceous and undermined.

Diagnosis of Pyoderma gangrenosum can be difficult. Diagnosis is often made by its characteristic appearance, associations with other diseases, the presence of pathergy, histology

results and when other diseases have been ruled out. Histology is not specific and can vary depending on time and site of the specimen. It is helpful in ruling out other causes of an ulcer. The ulcer should be swabbed and cultured for micro-organisms and fungi.

Treatment is mainly steroid (0.5-2mg/kg) therapy which is slowly tapered over 1-2 months. Immunosuppressants are useful as a steroid sparing agent and maintenance therapy. These may include ciclosporin, methotrexate, mycophenolate mofetil and cyclophosphamide. Surgery should be postponed until the disease process is controlled on immunosuppression to risk worsening of the disease (pathergy).

Necrobiosis lipoidica is a skin disorder which can affect the shins. This most commonly occurs in patients with insulin dependent diabetics, although it may occur in non-diabetic patients. These lesions are characteristically yellowish brown patches which appear slowly over a few months. The patch is often pale, shiny and has telangiectasia present. They are often painless. Ulceration can occur if the patch has a minor injury to the area.

Erythema nodosum is often described as red lumps that form on the shins, but can also occur on the forearms and thighs. It is an inflammatory disorder affecting subcutaneous fat (panniculitis). Patients commonly develop these in association with bacterial infections (commonly mycoplasma pneumonia), streptococcal throat infections, sarcoidosis, tuberculosis, drugs such as the oral contraceptive pill, NSAIDs and salicylates, pregnancy and inflammatory bowel disease.

The lesions may appear in a range of sizes and number. The nodules are often painful, warm and red on first appearance. Later they may change to a purple colour and appear more like a bruise. This bruise like colour often evolves over the next 1-2 weeks and then subsides by 3rd to 6th week. The patient may also complain of a fever, arthralgia and malaise.

## **Pyoderma gangrenosum**

### **Features**

- typically on the lower limbs
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

### **Causes\***

- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's

- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

## Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

\*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes



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### Question 3 of 135

A 33-year-old woman with a history of psoriasis presents with a 'rash' in both axillae.



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What is the most appropriate first-line treatment?

[Miconazole twice a day 14% Dithranol once a day 6% Calcipotriol twice a day 10% Eumovate \(clobetasone butyrate\) once a day 30% Calcipotriol + beclomethasone once a day 40%](#)

This patient has flexural psoriasis - a mild or moderately potent steroid should be used.

## **Psoriasis: management**

NICE released guidelines in 2012 on the management of psoriasis and psoriatic arthropathy. Please see the link for more details.

### **Management of chronic plaque psoriasis**

- regular emollients may help to reduce scale loss and reduce pruritus
- first-line: NICE recommend a potent corticosteroid applied once daily plus vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- second-line: if no improvement after 8 weeks then offer a vitamin D analogue twice daily
- third-line: if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a coal tar preparation applied once or twice daily
- short-acting dithranol can also be used





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### Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms
- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g. > 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

### What should I know about vitamin D analogues?

- examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



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A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

### Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

### Scalp psoriasis

- NICE recommend the use of potent topical corticosteroids used once daily for 4 weeks
- if no improvement after 4 weeks then either use a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or a topical agents to remove

adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

Face, flexural and genital psoriasis

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

## **Secondary care management**

Phototherapy

- narrow band ultraviolet B light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

Systemic therapy

- oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- ciclosporin
- systemic retinoids
- biological agents: infliximab, etanercept and adalimumab
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials

Mechanism of action of commonly used drugs:

- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Question 5 of 135

A 72-year-old woman is diagnosed with a number of erythematous, rough lesions on the back of her hands. A diagnosis of actinic keratoses is made. What is the most appropriate management?

[Reassurance7%](#)[Urgent referral to a dermatologist14%](#)[Topical fluorouracil cream65%](#)[Review in 3 months8%](#)[Topical betnovate7%](#)

## Actinic keratoses

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

### Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present

### Management options include

- prevention of further risk: e.g. sun avoidance, sun cream
- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

### Question 1 of 130

A 36-year-old presents with a 4 months history of episodic generalised abdominal discomfort, nausea and vomiting. He reports no gastrointestinal symptoms prior to this period. He denies eating any unusual foods or recent travel within the past 2 years. His diarrhoea appears to be watery and he denies any blood stools. Eight months ago, he underwent a bone densimetry scan after breaking his hip and both femurs playing football, revealing a T-score of  $<-2.8$ . On examination, you notice brown papules, measuring 2 to 3 mm on each lower leg. When you press along the lesion and the surrounding skin, you note a red raised line is elicited. Abdominal examination reveals hepatosplenomegaly. His admission blood tests are as follows:

Hb 98 g/l  
Platelets  $195 \times 10^9/l$   
WBC  $4.9 \times 10^9/l$   
ESR 70 mm/hr

Na <sup>+</sup>	138 mmol/l
K <sup>+</sup>	4.6 mmol/l
Adjusted calcium	2.81 mmol/l
Phosphate	1.3 mmol/l
CRP	22 mg/l
Serum tryptase	379 ng/ml (< 20)
Complement	normal
C1 inhibitor	normal
Serum gastrin	normal
24 hour urinary 5-HIAA	normal

What is the most likely unifying diagnosis?

[Zollinger-Ellison syndrome10%](#)[Carcinoid syndrome9%](#)[Hereditary angioedema7%](#)[Cutaneous mastocytosis14%](#)[Systemic mastocytosis60%](#)

Localised erythema and urticaria on scratching, rubbing or stroking of the skin as described is classically known as Darier's sign, a manifestation of mast cell mediator release following physical irritation, classically seen in mastocytosis, a disorder of excessive mast cells. The next distinction is whether this represents symptoms limited to the skin or involves extracutaneous sites, hence the classification of cutaneous and systemic mastocytosis respectively. Systemic symptoms are a result of mast cell mediator and IgE release, which can cause gastrointestinal, neuropsychiatric and anaphylactic symptoms. A mild anaemia, as in this patient, is common in half of all systemic mastocytosis patients. Infiltration of spleen, liver and lymph nodes are noted in physical examinations as organomegaly. Excessive bleeding can also be an issue as a result of excess heparin release from mast cells. Osteoporosis in young patients should make you suspicious of bone marrow involvement.

Diagnosis of cutaneous mastocytosis is made upon signs and symptoms alone. Systemic mastocytosis is diagnosed according to a WHO criteria of major and minor symptoms: the major criterion involves the presence of mast cells in extracutaneous organs such as the liver and bone marrow, while minor criteria relies on serum tryptase over 20, surface markers of mast cells, atypical bone marrow mast cell morphology and a specific kit mutation. In the case of this patient, serum tryptase is significantly elevated in association with systemic involvement.

An important differential is that of hereditary angioedema, caused by a deficiency of C1 inhibitor deficiency and transient painful episodes of skin, laryngeal and bowel oedema. In this case, C1 inhibitor and complement are normal. Similarly, carcinoid syndrome should produce increased

levels of urinary 24 hour 5HIAA secondary to excessive serotonin release. Lastly, Zollinger-Ellison syndrome only rarely presents with diarrhoea. Serum tryptase is almost always normal with elevated gastrin levels.

## **Systemic mastocytosis**

Systemic mastocytosis results from a neoplastic proliferation of mast cells

### Features

- urticaria pigmentosa - produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- monocytosis on the blood film

### Diagnosis

- raised serum tryptase levels
- urinary histamine

### Question 2 of 130

A 46-year-old lady presented to her general practitioner (GP) complaining of a rash across her abdomen. She had seen her GP a number of times in the preceding year feeling generally unwell, lethargic, having gained a significant amount of weight and developing irregular periods which had been attributed to the menopause. She had a previous medical history of bilateral carpal tunnel syndrome but took no regular medications. On examination, she was dressed in multiple layers of clothing, was overweight with dry skin and a localised area of reticulated erythema and hyper-pigmentation on her abdomen. Her temperature was 36.4 degrees Celsius, her pulse was 60 beats per minute and regular, her blood pressure was 100/55 mmHg and her respiratory rate was 16 breaths per minute.

### Investigations:

Haemoglobin 115 g/L

White cell count  $6.1 \times 10^9/L$

Platelet Count 268 x10<sup>9</sup>/L  
Serum sodium 130mmol/L  
Serum potassium 3.6mmol/L  
Serum urea 3.2mmol/L  
Serum creatinine 58micromol/L  
CRP 6 mmol/L

What is the most likely cause of the rash?

[Cellulitis4%Livedo reticularis23% Vasculitis4%Shingles4%Erythema ab igne65%](#)

This lady has presented with an abdominal rash but has also been systemically unwell for the last year with weight gain, lethargy and irregular periods. There a history of carpal tunnel syndrome and a suggestion of cold intolerance due to the multiple layers of clothing. These signs and symptoms suggest a clinical diagnosis of hypothyroidism.

Due to this lady's symptom and cold intolerance she has been applying regular hot water bottles to her abdomen which has led to the development of erythema ab igne. This is a skin condition which is caused by chronic exposure to heat and is commonly seen in patients with chronic pain who find relief from the application of heat, people who are chronically exposed to heat such as chefs, and hypothyroidism.

There is no evidence of infection or raised inflammatory markers to suggest cellulitis. Livedo reticularis causes a lace-like purple discolouration of the skin. It is caused by swollen venules due to blocked capillaries and can be idiopathic, normally in young women, or secondary to a systemic disease of which there are numerous causes including vasculitides, obstruction from clots (i.e. antiphospholipid syndrome) or emboli (typically cholesterol emboli following angiography). A vasculitis is unlikely as her inflammatory markers are normal and there is no other evidence of organ dysfunction. Shingles is caused by the reactivation of herpes zoster from a nerve root and occurs in the distribution of a dermatome which is not apparent in this case.

## **Erythema ab igne**

Erythema ab igne is a skin disorder caused by over exposure to infrared radiation. Characteristic features include reticulated, erythematous patches with hyperpigmentation and telangiectasia. A typical history would be an elderly women who always sits next to an open fire.

If the cause is not treated then patients may go on to develop squamous cell skin cancer.





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Erythema ab igne





## Erythema ab igne

### Question 1 of 127

A 55-year-old gentleman was referred to the urgent outpatient dermatology clinic with a flare up of long standing psoriasis. His GP had diagnosed him with psoriasis five years ago. It usually affected the extensor surfaces of his elbows and was well controlled with a combination of topical vitamin D analogue and topical corticosteroid. For the last four weeks, however, the rash had become extensive across his chest and back. Despite an intensive trial of topical high potency corticosteroid and further topical vitamin D analogue, his rash had seemed to be worsening, leading to his referral.

His past medical history comprised hypercholesterolaemia and hypertension which were diagnosed at a well man check by his GP three months ago. As he also suffered from palpitations which were thought to be induced by anxiety, he was commenced on propranolol modified release 80mg OD, as well as simvastatin 40mg OD. He also suffered from chronic low back pain for the last few years and used naproxen 500mg BD with lansoprazole 30mg OD for the last five years with good effect. He also admitted to using over the counter aspirin 75 mg OD for the last nine years as his friend was prescribed this by her doctor.

Examination revealed a widespread rash comprising of multiple scaly erythematous discrete plaques across his chest, abdomen, back and extensor surfaces of his elbows and knees. He was otherwise systemically well.

Which is the single most likely causative agent responsible for the deterioration?

[Propranolol60%Simvastatin11%Naproxen13%Lansoprazole7%Aspirin9%](#)

Psoriasis may be exacerbated by a variety of causes. With respect to drugs, the most common suspects are lithium and beta blockers. Other agents include antimalarials, ACE inhibitors and non-steroidal anti-inflammatories. The patient was indeed using naproxen and aspirin. However, he was commenced on propranolol recently with a subsequent exacerbation of his psoriasis. The most suitable answer, therefore, is propranolol.

### **Psoriasis: exacerbating factors**

The following factors may exacerbate psoriasis:

- trauma
- alcohol
- drugs: beta blockers, lithium, antimalarials (chloroquine and hydroxychloroquine), NSAIDs and ACE inhibitors, infliximab
- withdrawal of systemic steroids

Streptococcal infection may trigger guttate psoriasis.

#### Question 2 of 127

A 52-year-old male was referred to the outpatients dermatology clinic with a four-month history of a persistent rash. He described the rash as a very itchy blistering rash occurring on the popliteal fossa as well as his buttocks. He had been prescribed levocetirizine 5mg OD as well as a four-week course of Eumovate BD (moderately-potent corticosteroid) and Diprobase (emollient) QDS but despite the treatment his symptoms had worsened. He had a past medical history comprising refractory eczema, gout, angina, hypertension and diabetes mellitus type 2 for which he was prescribed allopurinol 100mg OD, aspirin 75mg OD, simvastatin 40mg OD, ramipril 5mg OD and metformin M/R 1g BD. Regarding his eczema, this is presently in a state of remission, having been treated with azathioprine six months ago. Other than the rash he was otherwise well though he mentioned he had a history of abdominal bloating and diarrhoea which was diagnosed as irritable bowel syndrome several years ago.

On examination, he was systemically well with a blood pressure of 142/76 mmHg. Examination of the cardiovascular, respiratory and gastrointestinal systems was unremarkable. Examination of his skin revealed the presence of multiple bullae and papules on the extensor surface of his knees and buttocks, with excoriation.

Which of the following is the most likely diagnosis?

[Bullous pemphigoid disease14%](#)[Linear IgA bullous dermatosis15%](#)[Dermatitis herpetiformis60%](#)[Transient acantholytic dermatosis6%](#)[Eczema5%](#)

This rash tends to present as an intensely itchy bullous rash comprising of blisters and papules on extensor surfaces, though can also occur on any other part of the body. This disease is strongly associated with uncontrolled coeliac disease, and the clue in this question is the presence of abdominal bloating and diarrhoea (red herring being diagnosed with irritable bowel syndrome, a common mistake to make in clinical practice!).

## Dermatitis herpetiformis

Dermatitis herpetiformis is an autoimmune blistering skin disorder associated with coeliac disease. It is caused by deposition of IgA in the dermis.

### Features

- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

### Diagnosis

- skin biopsy: direct immunofluorescence shows deposition of IgA in a granular pattern in the upper dermis

### Management

- gluten-free diet
- dapsone



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Question 3 of 127

A 60-year-old man presents with a painful lesion on his right ear:





What is the most likely diagnosis?

[Actinic keratosis6%](#)[Pseudocyst of the auricle6%](#)[Chondrodermatitis nodularis helices66%](#)[Basal cell carcinoma17%](#)[Keratoacanthoma6%](#)

### **Chondrodermatitis nodularis helices**

Chondrodermatitis nodularis helices (CNH) is a common and benign condition characterised by the development of a painful nodule on the ear. It is thought to be caused by factors such as persistent pressure on the ear (e.g. secondary to sleep, headsets), trauma or cold. CNH is more common in men and with increasing age.

#### **Management**

- reducing pressure on the ear: foam 'ear protectors' may be used during sleep
- other treatment options include cryotherapy, steroid injection, collagen injection
- surgical treatment may be used but there is a high recurrence rate

#### **Image gallery**





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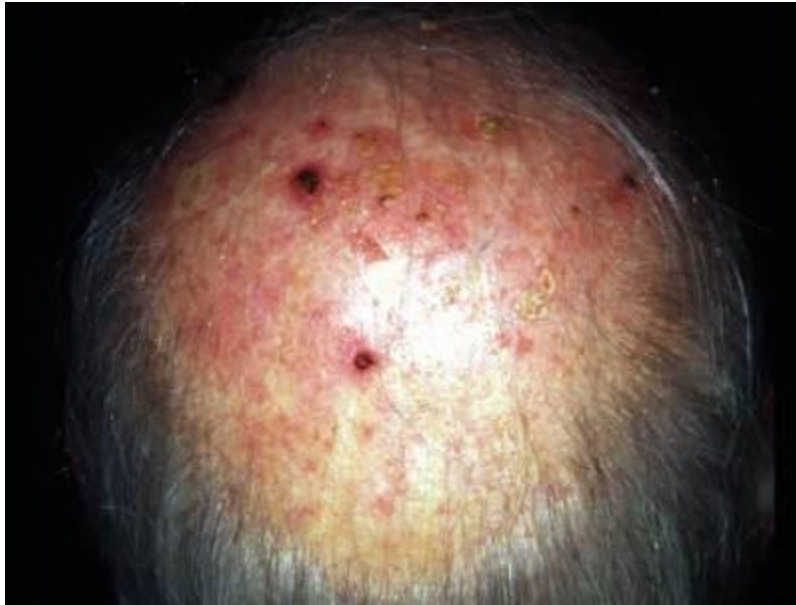
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You are asked to look at some skin lesions on a patient who has been admitted with an infective exacerbation of COPD.



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These skin lesions have been present for the past year. What is the most likely diagnosis?

[Multiple basal cell carcinomas4%](#) [Squamous cell carcinoma5%](#) [Actinic keratoses61%](#) [Seborrhoeic dermatitis14%](#) [Seborrhoeic keratoses17%](#)

## Actinic keratoses

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

### Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present



Management options include

- prevention of further risk: e.g. sun avoidance, sun cream
- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

Question 5 of 127

A 79-year-old woman presents with an itchy, blistering rash. Examination of her mouth is unremarkable.



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What is the most likely diagnosis?

[Dermatitis herpetiformis](#)4%[Drug reaction to lisinopril](#)5%[Bullous pemphigoid](#)68%[Pemphigus vulgaris](#)15%[Epidermolysis bullosa](#)8%

## Blisters/bullae

- no mucosal involvement (in exams at least\*): bullous pemphigoid
- mucosal involvement: pemphigus vulgaris

## **Bullous pemphigoid**

Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin. This is secondary to the development of antibodies against hemidesmosomal proteins BP180 and BP230

Bullous pemphigoid is more common in elderly patients. Features include

- itchy, tense blisters typically around flexures
- the blisters usually heal without scarring
- mouth is usually spared\*

## Skin biopsy

- immunofluorescence shows IgG and C3 at the dermoepidermal junction

## Management

- referral to dermatologist for biopsy and confirmation of diagnosis
- oral corticosteroids are the mainstay of treatment
- topical corticosteroids, immunosuppressants and antibiotics are also used



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\*in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.

#### Question 6 of 127

A 34-year-old man with a long history of back pain asks you to have a look at his back. His wife has noticed a rash.



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What is the most likely diagnosis?

[Pityriasis rosea4%](#)[Erythema multiforme4%](#)[Erythema ab igne81%](#)[Pityriasis versicolor6%](#)[Cold urticaria4%](#)

This is a typical erythema ab igne rash. He may have been applying a hot water bottle to his lower back to try and relieve the pain.

### **Erythema ab igne**

Erythema ab igne is a skin disorder caused by over exposure to infrared radiation. Characteristic features include reticulated, erythematous patches with hyperpigmentation and telangiectasia. A typical history would be an elderly women who always sits next to an open fire.

If the cause is not treated then patients may go on to develop squamous cell skin cancer.



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Erythema ab igne



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Erythema ab igne

Question 2 of 121

Please look at the skin lesion shown below:





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Which one of the following statements regarding this type of skin lesion is true?

[Curettage is an acceptable treatment option](#)46%[They exhibit the Koebner phenomenon](#)12%[They typically grow rapidly](#)11%[Bleeding is unusual](#)17%[Metastases are present in 10% of patients at the time of diagnosis](#)14%

## Basal cell carcinoma

Basal cell carcinoma (BCC) is one of the three main types of skin cancer. Lesions are also known as rodent ulcers and are characterised by slow-growth and local invasion. Metastases are extremely rare. BCC is the most common type of cancer in the Western world.

Features



- many types of BCC are described. The most common type is nodular BCC, which is described here
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia
- may later ulcerate leaving a central 'crater'

Management options:

- surgical removal
- curettage
- cryotherapy
- topical cream: imiquimod, fluorouracil
- radiotherapy





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### Question 3 of 121

A 35-year-old man asks you to review a lesion on his right arm. This has been present for the past six months but has not changed significantly over that period.



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What is the most likely diagnosis?

[Spitz naevus7%](#)[Dermatofibroma70%](#)[Nodular basal cell carcinoma6%](#)[Viral wart5%](#)[Dermoid cyst13%](#)

## **Dermatofibroma**

Dermatofibromas (also known as histiocytomas) are common benign fibrous skin lesions. They are caused by the abnormal growth of dermal dendritic histiocyte cells, often following a precipitating injury. Common areas include the arms and legs.

## **Image gallery**



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This image shows the 'pinch test'. A dimple is formed when a dermatofibroma is pinched indicating tethering of the skin to the underlying fibrous tissue

#### Question 7 of 121

A 74-year-old male presents to the acute medical take with left sided chest pain, worse on inspiration. On examination, you note his nails are yellow and clubbed with bilateral non-pitting oedema. Examination of his chest reveals reduced air entry of his left lung to mid zone, dull to percussion, with no wheeze.

He has a known past medical history of bronchiectasis diagnosed 2 years ago, for which he has been admitted 3 times in the past 5 months. He reports weight loss of about 8kg in the past 9 months. He last underwent an echocardiogram 2 years ago, during which a left ventricular ejection fraction of 56% was demonstrated.

A chest radiograph demonstrates a large left pleural effusion and a mark has been made by ultrasound for a pleural tap.

Pleural fluid analysis results are as follows:

pH	7.42
Protein	40 g/L (serum 58)
LDH	130 IU/L (serum 181)
Glucose	3.5 mmol/l (serum 6.2)



Amylase 22 u/l (serum 32)  
Triglycerides 1.90 mmol/L (serum 2.2)  
Cytology awaited  
AFB awaited

What is the unifying diagnosis?

[Parapneumonic effusion8% Yellow nail syndrome63%Malignant pleural effusion20%Oesophageal rupture4%Congestive cardiac failure6%](#)

Diagnosis here is dependent on subtle details in the history and pleural fluid analysis: the patient has bronchiectasis, pleural effusion (exudate), lymphoedema (not pitting oedema), chylothorax (note the significantly raised triglycerides in the pleural fluid) and of course, yellow nails! The patient has yellow nail syndrome, characterised by nail dystrophy or discolouration, lymphoedema and pleural effusions. A parapneumonic and malignant effusion are reasonable differentials but do not explain the triglycerides. Oesophageal rupture classically increases pleural amylase. Lastly, congestive cardiac failure classically produces a transudate.

## **Yellow nail syndrome**

Slowing of the nail growth leads to the characteristic thickened and discoloured nails seen in yellow nail syndrome.

Associations

- congenital lymphoedema
- pleural effusions
- bronchiectasis
- chronic sinus infections

Question 9 of 121

A 69-year-old woman asks you to have a look at her feet. She lives out in Spain most of the year but comes back to the UK periodically to see her family.



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She has similar changes on her forehead. The skin is not pruritic. What is the most likely diagnosis?

[Discoid lupus erythematosus6%](#) [Photosensitive eczema23%](#) [Porokeratosis17%](#) [Actinic keratoses46%](#) [Bowen's disease7%](#)

Actinic keratoses may develop on any sun-exposed area, not just the forehead and temple. Bowen's disease tends to be isolated and well demarcated.

## **Actinic keratoses**

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

### **Features**

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present

Management options include



- prevention of further risk: e.g. sun avoidance, sun cream
- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

#### Question 11 of 121

A 67-year-old man presents with a rough, scaly lesion on his nose. He has a long history of sun-related damage to his skin and has had similar lesions on his temples treated previously:



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Which one of the following is he at an increased risk of developing if the lesion is not treated?

[Pyoderma gangrenosum](#)3% [Seborrhoeic keratosis](#)15% [Malignant melanoma](#)5% [Basal cell carcinoma](#)11% [Squamous cell carcinoma](#)65%

Actinic keratoses are premalignant lesions which may develop into squamous cell carcinomas if not treated.

## **Actinic keratoses**

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

### Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
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### Management options include

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- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

### Question 14 of 121

A 75-year-old asks you to have a look at a lesion on his right ear. It has developed slowly over the past few months and is tender to palpation.



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What is the most likely diagnosis?

[Cystic chondromalacia](#)7% [Actinic keratosis](#)25% [Chondrodermatitis nodularis helicis](#)48% [Perichondritis](#)7% [Keratin horn](#)13%

### **Chondrodermatitis nodularis helicis**

Chondrodermatitis nodularis helicis (CNH) is a common and benign condition characterised by the development of a painful nodule on the ear. It is thought to be caused by factors such as persistent pressure on the ear (e.g. secondary to sleep, headsets), trauma or cold. CNH is more common in men and with increasing age.

#### **Management**

- reducing pressure on the ear: foam 'ear protectors' may be used during sleep
- other treatment options include cryotherapy, steroid injection, collagen injection
- surgical treatment may be used but there is a high recurrence rate

#### **Image gallery**



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Question 13 of 121

Please look at the image below:



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Which one of the following is LEAST likely to have a role in the management of this patient?

[Sun block9% Topical tacrolimus10% Phototherapy17% Topical ketoconazole54% Topical corticosteroids11%](#)

There is no role for antifungal therapy in vitiligo.

## **Vitiligo**

Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin. It is thought to affect around 1% of the population and symptoms typically develop by the age of 20-30 years.

### Features

- well demarcated patches of depigmented skin
- the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

### Associated conditions

- type 1 diabetes mellitus
- Addison's disease
- autoimmune thyroid disorders
- pernicious anaemia
- alopecia areata

### Management

- sun block for affected areas of skin
- camouflage make-up
- topical corticosteroids may reverse the changes if applied early
- there may also be a role for topical tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients



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#### Question 1 of 106

A 27-year-old man was seen in the dermatology clinic with an itchy, vesicular rash over buttocks and proximal forearms. He was otherwise well.

A subsequent skin biopsy and direct immunofluorescence demonstrate granular IgA at the dermal-epidermal junction. Given the most likely diagnosis, he was started on dapsone and given specific dietary advice.

Six weeks later he complains of worsening fatigue.

What is the most important investigation?

[Full blood count](#)68%[Echocardiogram](#)7%[ECG](#)4%[Urine protein:creatinine ratio](#)10%[Creatine kinase](#)12%

The patient has dermatitis herpetiformis - an inflammatory cutaneous condition closely associated with gluten sensitive enteropathy (coeliac disease).

Dapsone is an antibacterial agent that can provide temporary symptomatic relief as a gluten-free diet is established. The main side effect is that of haemolytic anaemia - so regular full blood counts are essential. Other side effects include peripheral neuropathy and rarely agranulocytosis.

The remaining options are clearly not correct if the candidate is aware of the side effects of dapsone - a MRCP favourite - as is the presentation of dermatitis herpetiformis without overt



diarrhoea.

Further reading:

BMJ Easily Missed: Dermatitis Herpetiformis

<http://www.bmj.com/content/348/bmj.g2557>

## **Dermatitis herpetiformis**

Dermatitis herpetiformis is an autoimmune blistering skin disorder associated with coeliac disease. It is caused by deposition of IgA in the dermis.

### Features

- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

### Diagnosis

- skin biopsy: direct immunofluorescence shows deposition of IgA in a granular pattern in the upper dermis

### Management

- gluten-free diet
- dapsone



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A 21-year-old woman with a history of eczema presents with a change in the colour of her skin affecting the hands and feet symmetrically:



What is the most likely diagnosis?

[Excessive topical corticosteroid use](#)10%[Leprosy](#)4%[Tuberous sclerosis](#)4%[Vitiligo](#)73%[Pityriasis versicolor](#)8%

## **Vitiligo**

Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin. It is thought to affect around 1% of the population and symptoms

typically develop by the age of 20-30 years.

### Features

- well demarcated patches of depigmented skin
- the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

### Associated conditions

- type 1 diabetes mellitus
- Addison's disease
- autoimmune thyroid disorders
- pernicious anaemia
- alopecia areata

### Management

- sun block for affected areas of skin
- camouflage make-up
- topical corticosteroids may reverse the changes if applied early
- there may also be a role for topical tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients



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### Question 1 of 103

A 47-year-old lady presented with shortness of breath and a nosebleed. She had been experiencing heavy nosebleeds over the past fifteen years and had twice required cauterization. On this admission she felt very tired, with shortness of breath and chest pain on minimal exertion.

Aside from nosebleeds she had a past medical history of hypertension and hypothyroidism. She had recently consulted a cosmetic surgeon privately as she had spider veins over her lips which she wished to have removed.

She lived with her husband who had been diagnosed with multiple sclerosis and her 18-year-old son who had learning difficulties and epilepsy. She reported that her mother and sister also experienced frequent nosebleeds.

On examination there was conjunctival pallor. The lung fields were clear on auscultation and both heart sounds were present with a systolic murmur audible over the aortic region. The abdomen was soft and non-tender with no palpable masses or organomegaly. On inspection of the skin there was a bruise in the left antecubital fossa and no rashes.

What is the most likely unifying diagnosis?

[Von Willebrand disease4%Wegeners granulomatosis4%Von Hippel Lindau disease7%Idiopathic Thrombocytopaenic Purpura3%Hereditary haemorrhagic telangiectasia81%](#)

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler Weber Rendu syndrome, is an autosomal dominant disorder leading to abnormal blood vessel formation in the skin, mucous membranes, liver, lungs and brain. In this case, both the patients mother, sister and son are also affected indicating a likely autosomal dominant inheritance. Telangiectasia, such as the ones on this patients lips, are found on mucosal surfaces and in the gastrointestinal tract. These can cause nosebleeds and this is the most common presentation of HHT. Nosebleeds and bleeding from telangiectasia in the gastrointestinal tract can lead to an iron deficiency anaemia which explains the shortness of breath, pallor, chest pain and flow murmur in this case. Other manifestations of HHT occur secondary to the formation of arteriovenous malformations (AVMs) and include haemoptysis, portal hypertension and oesophageal varices, congestive cardiac failure, headache, intracerebral haemorrhage and seizures. Treatment is largely symptomatic and anaemia is treated with transfusions and iron replacement.

Von Willebrand disease can present with nosebleeds and may be inherited in an autosomal dominant fashion. However, this diagnosis would not account for the severe symptomatic anaemia, telangiectasia or the neurological features in this patients son. Other features of von Willebrands disease include bleeding gums and purpura.

Wegeners granulomatosis is a form of vasculitis that can cause nosebleeds. It is not a genetic condition and other clinical manifestations include haemoptysis, rapidly progressive glomerulonephritis, arthritis and a purpuric rash.

Von Hippel Lindau disease is a rare autosomal dominant condition which is associated with many tumour types including haemangioblastomas, neuroendocrine tumours and renal cell carcinoma. It can present with walking difficulties, headaches and hypertension in addition to other symptoms and signs however nosebleeds are not a commonly recognised feature of this disease.

Idiopathic Thrombocytopaenic Purpura (ITP) is an autoimmune condition which can present with easy bruising, purpura and nosebleeds. In patients with ITP there is usually no family history and the condition does not cause telangiectasia.

### **Hereditary haemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



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The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

Question 2 of 103

A 23-year-old woman who is 10 weeks pregnant presents with a rapidly growing lesion on her finger. This has grown from the size of a 'pin-prick' when it first appeared 4 weeks ago.





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What is the most likely diagnosis?

[Viral wart9%](#)[Orf14%](#)[Pyogenic granuloma57%](#)[Capillary haemangioma10%](#)[Squamous cell carcinoma10%](#)

## **Pyogenic granuloma**

Pyogenic granuloma is a relatively common benign skin lesion. The name is confusing as they are neither true granulomas nor pyogenic in nature. There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.

The cause of pyogenic granuloma is not known but a number of factors are linked:

- trauma
- pregnancy
- more common in women and young adults

Features

- most common sites are head/neck, upper trunk and hands. Lesions in the oral mucosa are common in pregnancy
- initially small red/brown spot
- rapidly progress within days to weeks forming raised, red/brown lesions which are often spherical in shape
- the lesions may bleed profusely or ulcerate

## Management

- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist. Removal methods include curettage and cauterisation, cryotherapy, excision



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Question 4 of 103

A middle aged man develops a non-pruritic rash after starting allopurinol therapy for gout. The rash develop within 24 hours and started on the back of his hands.



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What is the most likely diagnosis?

[Allopurinol-associated dermatitis](#)8%[Plaque-type tophi](#)5%[Erythema multiforme](#)70%[Erythema marginatum](#)7%[Eosinophilic folliculitis](#)10%

## **Erythema multiforme**

Erythema multiforme is a hypersensitivity reaction which is most commonly triggered by infections. It may be divided into minor and major forms.

Previously it was thought that Stevens-Johnson syndrome (SJS) was a severe form of erythema multiforme. They are now however considered as separate entities.

### **Features**

- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild

## Causes

- viruses: herpes simplex virus (the most common cause), Orf\*
- idiopathic
- bacteria: *Mycoplasma*, *Streptococcus*
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus
- sarcoidosis
- malignancy



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## **Erythema multiforme major**

The more severe form, erythema multiforme major is associated with mucosal involvement.





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Example of mucosal involvement in erythema multiforme major

\*Orf is a skin disease of sheep and goats caused by a parapox virus

#### Question 5 of 103

A 12-year-old boy is brought with a persistent 'scab' above his right ear. His mother reports that it has slowly developed over the past few weeks and initially started out as a patch of 'dandruff'. He is systemically well and there is no past medical history of note. The lesion is shown below:





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What is the most likely diagnosis?

[Seborrhoeic dermatitis](#)22% [Trichotillomania](#)10% [Impetigo](#)10% [Scalp psoriasis](#)9% [Kerion](#)50%

The kerion has developed as a result of an untreated tinea capitis infection. Systemic antifungals are usually required.

## **Tinea**

Tinea is a term given to dermatophyte fungal infections. Three main types of infection are described depending on what part of the body is infected

- tinea capitis - scalp
- tinea corporis - trunk, legs or arms
- tinea pedis - feet

Tinea capitis (scalp ringworm)

- a cause of scarring alopecia mainly seen in children

- if untreated a raised, pustular, spongy/boggy mass called a kerion may form
- most common cause is *Trichophyton tonsurans* in the UK and the USA
- may also be caused by *Microsporum canis* acquired from cats or dogs
- diagnosis: lesions due to *Microsporum canis* green fluorescence under Wood's lamp\*. However the most useful investigation is scalp scrapings
- management (based on CKS guidelines): oral antifungals: terbinafine for *Trichophyton tonsurans* infections and griseofulvin for *Microsporum* infections. Topical ketoconazole shampoo should be given for the first two weeks to reduce transmission



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Image showing a kerion

Tinea corporis (ringworm)

- causes include *Trichophyton rubrum* and *Trichophyton verrucosum* (e.g. From contact with cattle)
- well-defined annular, erythematous lesions with pustules and papules
- may be treated with oral fluconazole



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Image showing tinea corporis



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Image showing tinea corporis. Note the well defined border

Tinea pedis (athlete's foot)

- characterised by itchy, peeling skin between the toes
- common in adolescence

\*lesions due to *Trichophyton* species do not readily fluoresce under Wood's lamp

Question 6 of 103

A 50-year-old male patient with a history of severe psoriasis has previously tried treatment with topical corticosteroids, vitamin D analogue therapy and phototherapy with little effect.

On examination he has multiple well circumscribed indurated erythematous plaques with overlying white scale over the majority of the trunk and forearms.

Blood tests reveal:

Hb	135 g/l
Platelets	$405 \times 10^9/l$
WBC	$8.2 \times 10^9/l$
Bilirubin	12 $\mu\text{mol/l}$
ALP	70 u/l
ALT	27 u/l
Albumin	35 g/l
Na <sup>+</sup>	140 mmol/l
K <sup>+</sup>	5.1 mmol/l
Urea	8.2 mmol/l
Creatinine	112 $\mu\text{mol/l}$

What is the most appropriate therapy?

[Infliximab13%Adalimumab9%Ciclosporin16%Methotrexate49%Etanercept13%](#)

NICE CG154 addresses the approach to systemic therapy for psoriasis and is outlined below:

Offer systemic non-biological therapy to people with any type of psoriasis if:

- It cannot be controlled with topical therapy and
- It has a significant impact on physical, psychological or social wellbeing and one or more of the following apply:

psoriasis is extensive (for example, more than 10% of body surface area affected or a PASI score of more than 10) or

psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) or

phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

Choice of drugs:

- Offer methotrexate as the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy (above)
- Offer ciclosporin as the first choice of systemic agent for people who fulfil the criteria for systemic therapy (above) and who:

need rapid or short-term disease control (for example a psoriasis flare) or

have palmoplantar pustulosis or

are considering conception (both men and women) and systemic therapy cannot be avoided.

- Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate.
- Consider acitretin for adults, and in exceptional cases only for children and young people, in the following circumstances:

if methotrexate and ciclosporin are not appropriate or have failed or for people with pustular forms of psoriasis.

## **Psoriasis: management**

NICE released guidelines in 2012 on the management of psoriasis and psoriatic arthropathy. Please see the link for more details.

Management of chronic plaque psoriasis

- regular emollients may help to reduce scale loss and reduce pruritus
- first-line: NICE recommend a potent corticosteroid applied once daily plus vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- second-line: if no improvement after 8 weeks then offer a vitamin D analogue twice daily
- third-line: if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a coal tar preparation applied once or twice daily
- short-acting dithranol can also be used





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### Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms

- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g. > 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

What should I know about vitamin D analogues?

- examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



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A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

### Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

### Scalp psoriasis

- NICE recommend the use of potent topical corticosteroids used once daily for 4 weeks
- if no improvement after 4 weeks then either use a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or a topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

### Face, flexural and genital psoriasis

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

## Secondary care management

### Phototherapy

- narrow band ultraviolet B light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

### Systemic therapy

- oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- ciclosporin
- systemic retinoids

- biological agents: infliximab, etanercept and adalimumab
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials

Mechanism of action of commonly used drugs:

- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Question 9 of 103

This woman complains of a 'rash' on her cheeks. She has recently started taking hormone replacement therapy for menopausal symptoms.



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What is the most likely diagnosis?

[Viligo](#)11%[Seborrhoeic dermatitis](#)6%[Acne rosacea](#)11%[Melasma](#)66%[Systemic lupus erythematosus](#)6%

## Melasma

Melasma is a condition associated with the development of hyperpigmented macules in sun-exposed areas, particularly the face. The term chloasma is sometimes used interchangeably but more specifically describes the appearance of melasma during pregnancy.

### Epidemiology

- more common in women
- more common in people with darker skin

### Causes

- pregnancy
- combined oral contraceptive pill, hormone replacement therapy



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A 27-year-old woman who is 34 weeks pregnant presents with an itchy, blistering rash over her abdomen. Initially she had a red rash around her umbilicus but it later spread.



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What is the most likely diagnosis?

[Pemphigoid gestationis](#)59%[Seborrhoeic dermatitis](#)4%[Polymorphic eruption of pregnancy](#)27%[HELLP syndrome](#)4%[Pompholyx](#)6%

## **Skin disorders associated with pregnancy**

### **Polymorphic eruption of pregnancy**

- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used



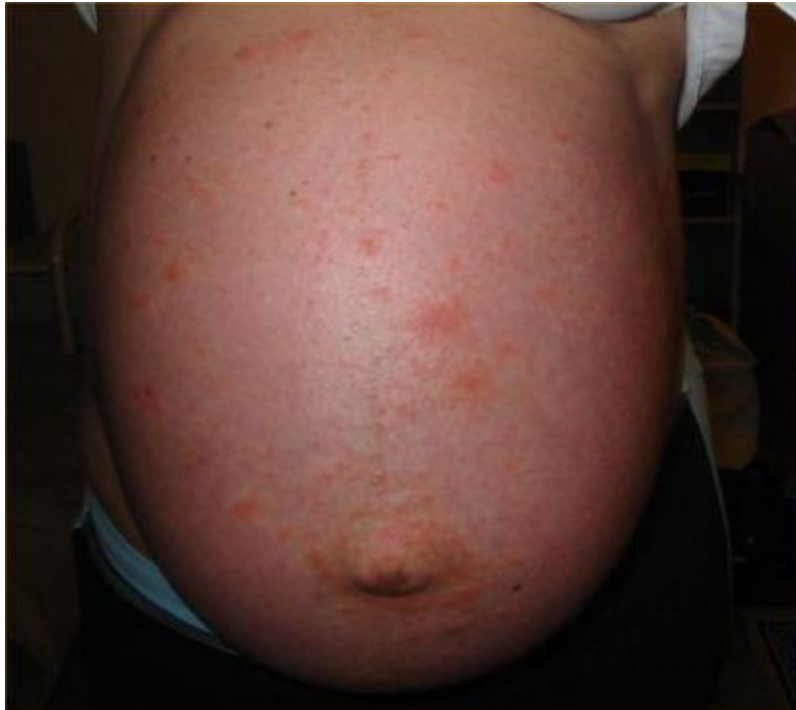
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Polymorphic eruption of pregnancy





## Polymorphic eruption of pregnancy



## Polymorphic eruption of pregnancy

### Pemphigoid gestationis

- pruritic blistering lesions
- often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
- usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- oral corticosteroids are usually required



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Pemphigoid gestationis



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Pemphigoid gestationis



A 82-year-old man is reviewed in dermatology clinic as part of ongoing treatment for metastatic melanoma. He had been diagnosed with melanoma three years previously after resection of a lesion on his left shoulder. Surgical margins had been satisfactory, however a metastatic lesion had been identified in the patient's liver four months prior to the present day. Following oncology MDT discussion, patient had been treated with vemurafenib. Initial follow-up with repeat abdominal CT scan had demonstrated an excellent response with dramatic reduction in size of metastatic deposit.

The patient reported continuing to feel well in himself. However, he was concerned about a new skin lesion he had noticed on his right thigh. While he could not recall exactly when this lesion had first appeared, he was confident that it had been present for less than two months. It had not been present during a full dermatological examination at the previous clinic appointment three months previously. The patient reported that the lesion was a bit uncomfortable when he caught it on his trousers but denied any other symptoms.

Examination of the lesion on the patient's thigh revealed a 11 mm diameter erythematous papule with minimally everted edges. A slight scale was noted on the surface of the lesion. There was no evidence of telangiectasia associated with the lesion. Examination of the inguinal lymph nodes was unremarkable.

Following assessment in clinic, a biopsy of the lesion was taken. What is the most likely diagnosis following histological examination of the biopsy specimen?

[Melanoma9% Merkel cell carcinoma14% Squamous cell carcinoma40% Atypical fibroxanthoma12% Keratocanthoma25%](#)

Vemurafenib and dabrafenib are selective BRAF inhibitors that increase overall survival in metastatic melanoma. These drugs paradoxically activates the MAPK pathway in keratinocytes and so can cause squamous cell carcinomas, often within the first three months of therapy. The risk of squamous cell carcinoma with vemurafenib and dabrafenib is higher in older patients and they can occur in sun-protected sites.

Given the typical appearance of the above lesion and the recent treatment with vemurafenib, the most likely histology of the lesion in this case is squamous cell carcinoma. Melanoma is less likely due to the atypical appearance and apparent good treatment response to vemurafenib.

The description of the lesion is not consistent with the typical appearance of the other possible answers.

Aslam A, Patel A. Facial cutaneous squamous cell carcinoma. BMJ 2016;352:i1513.

**Squamous cell carcinoma of the skin**



Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

### Image gallery



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## Treatment

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## Prognosis

### Good Prognosis

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### Poor prognosis

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason

Question 16 of 103

A 32-year-old lady attends with a facial rash for several weeks. She has an erythematous rash which looks greasy and has a fine scale over her face affecting her cheeks, nasolabial folds, eyebrows, nasal bridge and scalp. What is the most likely diagnosis?

[Acne rosacea](#)25%[Systemic lupus erythematosus \(SLE\)](#)8%[Eczema](#)4%[Seborrhoeic dermatitis](#)57%[Psoriasis](#)6%

The description describes seborrhoeic dermatitis. The involvement of the nasolabial folds

differentiates it from acne rosacea which typically spares this area and tends to include telangiectasia and pustules.

## **Seborrhoeic dermatitis in adults**

Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called *Malassezia furfur* (formerly known as *Pityrosporum ovale*). It is common, affecting around 2% of the general population

### Features

- eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- otitis externa and blepharitis may develop

### Associated conditions include

- HIV
- Parkinson's disease

### Scalp disease management

- over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- the preferred second-line agent is ketoconazole
- selenium sulphide and topical corticosteroid may also be useful

### Face and body management

- topical antifungals: e.g. Ketoconazole
- topical steroids: best used for short periods
- difficult to treat - recurrences are common

Question 17 of 103

A 36-year-old man presents to the Emergency Department. He is known to have a history of chronic plaque psoriasis and asthma. He has recently finished a course of prednisolone following a viral exacerbation of his asthma. He has reasonable control of his psoriasis using Dovobet ointment (betamethasone + calcipotriol) but you note that he has been using it almost continually for the past 2-3 months.

Over the past 24 hours he has developed a generalised erythematous rash. He reports feeling generally unwell. The heart rate is 90/min and his temperature is 37.3°.



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What is the most appropriate next step?

[Admit to dermatology63%](#)[Restart oral prednisolone17%](#)[Perform a HIV test6%](#)[Perform a urine dipstick7%](#)[Switch from current topical treatment to very potent topical corticosteroids8%](#)

The generalised erythematous rash and systemic upset points to a diagnosis of erythroderma. He should therefore be admitted to dermatology. This presentation may have been precipitated by the stopping of prednisolone.

## Erythroderma



Erythroderma is a term used when more than 95% of the skin is involved in a rash of any kind.

#### Causes of erythroderma

- eczema
- psoriasis
- drugs e.g. gold
- lymphomas, leukaemias
- idiopathic

#### Erythrodermic psoriasis

- may result from progression of chronic disease to an exfoliative phase with plaques covering most of the body. Associated with mild systemic upset
- more serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management



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This image shows the generalised erythematous rash seen in patients with erythroderma, sometimes referred to as 'red man syndrome'



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Note the extensive exfoliation seen in this patient

#### Question 18 of 103

A 58 year-old man is referred to the clinic with chronic diarrhoea and episodes of facial flushing. A computed tomography scan of her chest and abdomen reveal she has a neuroendocrine carcinoma of the appendix, causing carcinoid syndrome.

She refuses treatment and presents six months later having been referred by a neurologist as having early onset dementia and a rapidly evolving photosensitive rash on her trunk and upper arms.

Which of the following is the most likely diagnosis?

[Systemic lupus erythematosus5%](#) [Herpes Zoster infection4%](#) [Pellagra76%](#) [Wernicke-Korsakoff syndrome5%](#) [Porphyria11%](#)

The most likely diagnosis in this case is pellagra, a vitamin deficiency disease most frequently caused by a chronic lack of niacin (vitamin B3). In carcinoid syndrome, neuroendocrine tumours



along the GI tract use tryptophan as the source for serotonin production, which limits the available tryptophan for niacin synthesis, thus carcinoid syndrome produces a niacin deficiency.

## Pellagra

Pellagra is caused by nicotinic acid (niacin) deficiency. The classical features are the 3 D's - dermatitis, diarrhoea and dementia

Pellagra may occur as a consequence of isoniazid therapy (isoniazid inhibits the conversion of tryptophan to niacin) and it is more common in alcoholics.

### Features

- dermatitis (brown scaly rash on sun-exposed sites - termed Casal's necklace if around neck)
- diarrhoea
- dementia, depression
- death if not treated

### Question 19 of 103

A 16-year-old male is investigated for recurrent epistaxis, haemoptysis and iron-deficiency anaemia. Blood tests show the following:

Hb 11.1 g/dl  
Platelets  $341 \times 10^9/l$   
WBC  $4.3 \times 10^9/l$

Bilirubin 33  $\mu\text{mol/l}$   
ALP 131 u/l  
ALT 54 u/l  
 $\gamma\text{GT}$  135 u/l  
Albumin 40 g/l

A chest x-ray and CT abdomen are requested:



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What is the most likely diagnosis?

[Acute lymphoblastic leukaemia](#)6% [Metastatic cancer secondary to familial adenomatous polyposis](#)4% [Hereditary haemorrhagic telangiectasia](#)77% [Metastatic pleuropulmonary blastoma](#)5% [Peutz-Jeghers syndrome](#)9%

## **Hereditary haemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



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The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

Question 20 of 103

An elderly man presents with a lesion on his cheek that has got progressively worse over the past year. He asks for it to be removed as it is catching:



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What is the most likely diagnosis?

[Nodular malignant melanoma](#)10% [Viral wart](#)8% [Solar keratosis](#)16% [Seborrhoeic keratosis](#)24% [Squamous cell carcinoma](#)42%

The main differential diagnosis here is keratoacanthoma which are often described as 'mini-volcanos' with a central core filled with keratin.

### **Squamous cell carcinoma of the skin**

Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

## Image gallery



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## **Treatment**

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## **Prognosis**



### **Good Prognosis**

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### **Poor prognosis**

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason

### Question 1 of 83

A 21-year-old woman presents to the emergency department with an itchy rash. It developed over the course of the day which she spent at the beach with friends.

She complains of an itching and burning sensation on her upper arms, trunk and thighs.

On examination there are crops of 3mm pink papules over the symptomatic areas, sparing her face and her hands.

What is the most likely diagnosis?

[Scabies5%Systemic lupus erythematosus4%Xeroderma pigmentosum10%Photoallergic contact dermatitis27%Polymorphic light eruption54%](#)

Photoallergic contact dermatitis is a toxic or allergic reaction that occurs when certain chemicals are applied to the skin and subsequently exposed to the sun. It is unlikely to spare the hands and face.

Xeroderma pigmentosum is a rare hereditary defect of the enzyme system that repairs DNA after damage from ultraviolet rays, resulting in extreme sensitivity to sunlight and a tendency to develop skin cancer. It typically presents in youth with multiple basal cell carcinomas and other skin malignancies.

The photosensitive rash of systemic lupus erythematosus classically includes the butterfly-shaped rash that appears over the bridge of the nose and both cheeks.

The rash associated with scabies often appears as erythematous papules on the trunk and limbs with vesicles on palms and soles and irregular tracks in the web spaces between the fingers.

### **Polymorphic light eruption**

Polymorphic light eruption (PLE) is a common form of primary photosensitivity that mainly occurs in young adult women in temperate climates during spring and summer.

The name polymorphic refers to the fact that the rash can take many forms, although in one individual it usually looks the same every time it appears.

In most affected individuals, it occurs each spring, provoked by several hours outside on a sunny day. If further sun exposure is avoided, the rash settles in a few days.

The arms, the back of the hands, the V of the neck, the chest and lower legs/feet may be affected, but the face is usually spared.

Question 2 of 83

An elderly man develops a generalised pruritic rash:



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Which one of the following is the mainstay of treatment?

[Gluten free diet6%](#)[Phototherapy4%](#)[Oral corticosteroids73%](#)[Long-term oral antibiotics4%](#)[Potent topical corticosteroids13%](#)

## **Bullous pemphigoid**

Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin. This is secondary to the development of antibodies against hemidesmosomal proteins BP180 and BP230

Bullous pemphigoid is more common in elderly patients. Features include

- itchy, tense blisters typically around flexures
- the blisters usually heal without scarring
- mouth is usually spared\*

Skin biopsy

- immunofluorescence shows IgG and C3 at the dermoepidermal junction

Management

- referral to dermatologist for biopsy and confirmation of diagnosis
- oral corticosteroids are the mainstay of treatment
- topical corticosteroids, immunosuppressants and antibiotics are also used



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\*in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.

Question 3 of 83

A 30-year-old man is investigated for recurrent nose bleeds and iron deficiency anaemia. You notice a number of erythematous lesions on his skin:



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What is the most likely underlying diagnosis?

[Peutz-Jeghers syndrome](#)12% [Alcohol excess](#)5% [Hereditary haemorrhagic telangiectasia](#)73% [Haemophilia A](#)4% [Idiopathic thrombocytopenic purpura](#)6%

### **Hereditary haemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible

diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



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The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

Question 4 of 83

A 43-year-old woman comes for review. A few months ago she developed redness around her nose and cheeks. This is worse after drinking alcohol. She is concerned as one of her work colleagues asked her if she had a drink problem despite her drinking 10 units per week.



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What is the most likely diagnosis?

[Mitral stenosis](#)5%[Seborrhoeic dermatitis](#)7%[Alcohol-related skin changes](#)5%[Acne rosacea](#)71%[Systemic lupus erythematosus](#)12%

This is a typical history of acne rosacea.

**Acne rosacea**

Acne rosacea is a chronic skin disease of unknown aetiology

#### Features

- typically affects nose, cheeks and forehead
- flushing is often first symptom
- telangiectasia are common
- later develops into persistent erythema with papules and pustules
- rhinophyma
- ocular involvement: blepharitis

#### Management

- topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques)
- more severe disease is treated with systemic antibiotics e.g. Oxytetracycline
- recommend daily application of a high-factor sunscreen
- camouflage creams may help conceal redness
- laser therapy may be appropriate for patients with prominent telangiectasia

#### Question 5 of 83

A 34-year-old who has recently returned from a business trip to New York presents with a one-day history of a painful rash on his neck:





What is the most appropriate management?

[Topical fusidic acid 12% Topical clotrimazole + hydrocortisone 10% Oral aciclovir + prednisolone 14% Oral aciclovir 54% Send blood for antibodies to \*Borrelia burgdorferi\* 11%](#)

One of the main clues in the question is the combination of a rash with pain. Other than shingles, there are not many conditions which cause both.

Whilst there is some evidence that systemic steroids speed up the healing of shingles, consensus guidelines do not advocate their use as adverse effects probably outweigh potential benefits.

## **Herpes zoster**

Shingles is an acute, unilateral, painful blistering rash caused by reactivation of the Varicella Zoster Virus (VZV).

## **The 'shingles vaccine'**

In 2013 the NHS introduced a vaccine to boost the immunity of elderly people against herpes zoster. Some important points about the vaccine:

- offered to all patients aged 70-79 years\*
- is **live-attenuated** and given **sub-cutaneously**

As it is a live-attenuated vaccine the main contraindications are immunosuppression.

Side-effects

- injection site reactions
- less than 1 in 10,000 individuals will develop chickenpox

### **Management of shingles**

Oral aciclovir is first-line. One of the main benefits of treatment is a reduction in the incidence of post-herpetic neuralgia.



\*there is also a catch up campaign. The following is taken from the NHS vaccination website:

*Anyone aged 70 can have the shingles vaccine on the NHS. You become eligible for the vaccine from the first day of September after your 70th birthday.*

*From September 1 2015, the shingles vaccine will be offered routinely to people aged 70 and, as a catch up, to those aged 78. You become eligible for the vaccine on the first day of September 2015 after you've turned 70 or 78.*

*In addition, anyone who was eligible for immunisation in the previous two years of the programme but missed out on their vaccinations remains eligible until their 80th birthday. This includes:*

- *people aged 71 and 72 on 1 September 2015*
- *people aged 79*

*The shingles vaccine is not available on the NHS to anyone aged 80 and over because it seems to be less effective in this age group.*

Question 6 of 83

This 21-year-old woman has a history of recurrent epistaxis:



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What is the most likely underlying diagnosis?

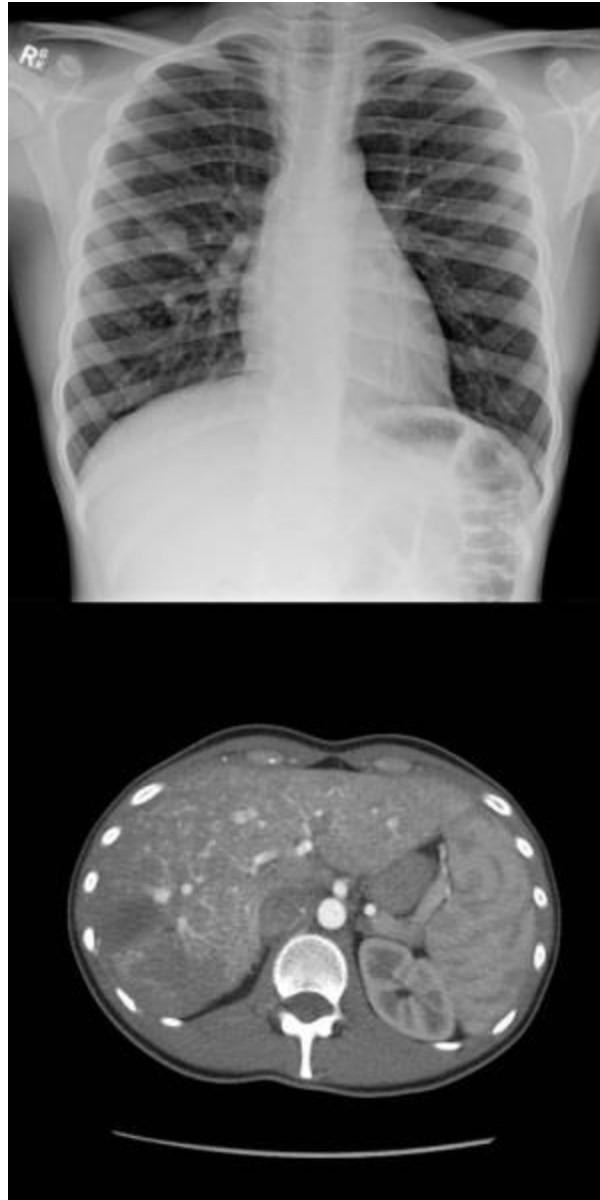
Idiopathic thrombocytopenic purpura7%Peutz-Jeghers syndrome13%Anorexia nervosa5%Combined oral contraceptive pill use4%Hereditary haemorrhagic telangiectasia72%

### **Hereditary haemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

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- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



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The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

Question 7 of 83

A 31-year-old man develops an erythematous rash overnight:



Which one of the following conditions is most strongly associated with this type of rash?

[Crohn's disease 13%](#) [Tuberculosis 5%](#) [Sarcoidosis 12%](#) [Herpes simplex virus 43%](#) [Staphylococcal infections 27%](#)

This is difficult as there are many possible triggers for erythema multiforme. However, studies suggest that HSV is the trigger in over 50% of cases. Sarcoidosis is more strongly associated with erythema nodosum.

## **Erythema multiforme**

Erythema multiforme is a hypersensitivity reaction which is most commonly triggered by infections. It may be divided into minor and major forms.

Previously it was thought that Stevens-Johnson syndrome (SJS) was a severe form of erythema multiforme. They are now however considered as separate entities.

### **Features**

- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild

## Causes

- viruses: herpes simplex virus (the most common cause), Orf\*
- idiopathic
- bacteria: *Mycoplasma*, *Streptococcus*
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus
- sarcoidosis
- malignancy



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### **Erythema multiforme major**

The more severe form, erythema multiforme major is associated with mucosal involvement.



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Example of mucosal involvement in erythema multiforme major

\*Orf is a skin disease of sheep and goats caused by a parapox virus

Question 9 of 83

A 65-year-old Caucasian lady presents with a new skin lesion to the forearm which has been present for 4 weeks. She reports she first noticed it after sustaining a minor abrasion to the area, and it has quickly increased in size since. On examination, there is a 10mm raised, symmetrical nodular lesion, which has a large keratinised central core. The surrounding skin appears normal, with no other similar lesions. What is the most likely diagnosis?

[Basal cell carcinoma](#)5% [Actinic keratosis](#)9% [Pyogenic granuloma](#)18% [Molluscum contagiosum](#)4% [Keratoacanthoma](#)64%

Keratoacanthoma are fast-growing skin lesions which may appear in areas of sun damaged skin. They may also develop after a minor skin injury. They typically start as a small, round fleshy nodule before developing a keratinised central core. Though they may spontaneously regress, they are difficult to distinguish clinically from a squamous cell carcinoma, and therefore should be referred for surgical removal.

Basal cell carcinomas tend to be slow growing lesions. Actinic keratoses tend to be scaly plaques. Pyogenic granuloma is another fast growing lesion which occur at the site of minor skin

injury, but are vascular, bleeding easily. Molluscum contagiosum are round lesions with a small central punctum caused by a pox virus that tend to appear in crops, mainly in children.

## **Keratoacanthoma**

Keratoacanthoma is a benign epithelial tumour. They are more frequent in middle age and do not become more common in old age (unlike basal cell and squamous cell carcinoma)

Features - said to look like a volcano or crater

- initially a smooth dome-shaped papule
- rapidly grows to become a crater centrally-filled with keratin

Spontaneous regression of keratoacanthoma within 3 months is common, often resulting in a scar. Such lesions should however be urgently excised as it is difficult clinically to exclude squamous cell carcinoma. Removal also may prevent scarring.



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### Question 10 of 83

A 22 year old female with a background history of iron deficient anaemia and eczema presents with a skin rash. She takes ferrous sulphate 200mg twice daily but no other medication. On examination she has an itchy bullous rash consisting of papules and blisters on the knees and elbows. Direct immunofluorescence of a skin biopsy shows immunoglobulin A (IgA) deposition in a granular pattern within the upper dermis. Which of the following would be the most appropriate treatment?

[Emollients and topical hydrocortisone 8%](#) [Dapsone and a gluten-free diet 61%](#) [Oral steroids 9%](#) [Emollients and a vitamin D analogue 7%](#) [A gluten-free diet and topical hydrocortisone 16%](#)

The clue here is the history of a young person who is iron-deficient and develops a rash which is not typical of eczema or psoriasis. Coeliac disease can often present with iron deficiency and no bowel manifestations and practitioners are lucky if their patient develops the characteristic rash of dermatitis herpetiformis, pointing them to the diagnosis.

## Dermatitis herpetiformis

Dermatitis herpetiformis is an autoimmune blistering skin disorder associated with coeliac disease. It is caused by deposition of IgA in the dermis.

### Features

- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

### Diagnosis

- skin biopsy: direct immunofluorescence shows deposition of IgA in a granular pattern in the upper dermis

### Management

- gluten-free diet
- dapsone



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Question 1 of 73

A 74-year-old man develops a painful blistering skin rash on his abdomen. He also complains of a sore throat, pain on swallowing and ulceration of the mouth:



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What is the most appropriate treatment?

[Oral prednisolone 64%](#) [Supportive treatment only 11%](#) [Intravenous flucloxacillin 10%](#) [Oral dapsone 7%](#) [Intravenous aciclovir 8%](#)

This patient has developed pemphigus vulgaris which is treated in the first instance by corticosteroids.

### **Pemphigus vulgaris**

Pemphigus vulgaris is an autoimmune disease caused by antibodies directed against desmoglein 3, a cadherin-type epithelial cell adhesion molecule. It is more common in the Ashkenazi Jewish population

## Features

- mucosal ulceration is common and often the presenting symptom. Oral involvement is seen in 50-70% of patients
- skin blistering - flaccid, easily ruptured vesicles and bullae. Lesions are typically painful but not itchy. These may develop months after the initial mucosal symptoms. Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin
- acantholysis on biopsy



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Mucosal ulceration is common with pemphigus



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## Management

- steroids
- immunosuppressants

### Question 2 of 73

A 36-year-old female with a history of ulcerative colitis is diagnosed as having pyoderma gangrenosum. She presented 4 days ago with a 3 cm lesion on her right shin which rapidly ulcerated and is now painful:



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What is the most appropriate management?

[Topical hydrocortisone 11%](#) [Oral prednisolone 53%](#) [Surgical debridement 11%](#) [Topical tacrolimus 9%](#) [Intravenous pulsed methylprednisolone 16%](#)

Topical therapy does have a role in pyoderma gangrenosum and it may seem intuitive to try this first before moving on to systemic treatment. However, pyoderma gangrenosum has the potential to evolve rapidly and for this reason oral prednisolone is usually given as initial treatment. For a review see BMJ 2006;333:181-184

## **Pyoderma gangrenosum**

### **Features**

- typically on the lower limbs
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

### **Causes\***

- idiopathic in 50%

- inflammatory bowel disease: ulcerative colitis, Crohn's
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

## Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

\*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes



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#### Question 4 of 73

A 28-year-old woman with a history of psoriasis presents with dandruff and an itchy scalp. She has tried using 'Head & Shoulders' with limited effect. A photograph of her scalp problems is shown below:





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What is the most appropriate first-line treatment?

[A coal tar based shampoo17%](#)[A ketoconazole based shampoo28%](#)[Topical beclomethasone22%](#)[Topical calcipotriol17%](#)[Topical calcipotriol + beclomethasone26%](#)

Scalp psoriasis - first-line treatment is topical potent corticosteroids

## **Psoriasis: management**

NICE released guidelines in 2012 on the management of psoriasis and psoriatic arthropathy. Please see the link for more details.

Management of chronic plaque psoriasis

- regular emollients may help to reduce scale loss and reduce pruritus

- first-line: NICE recommend a potent corticosteroid applied once daily plus vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- second-line: if no improvement after 8 weeks then offer a vitamin D analogue twice daily
- third-line: if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a coal tar preparation applied once or twice daily
- short-acting dithranol can also be used



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#### Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms
- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g. > 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

#### What should I know about vitamin D analogues?

- examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



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A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

### Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

### Scalp psoriasis

- NICE recommend the use of potent topical corticosteroids used once daily for 4 weeks
- if no improvement after 4 weeks then either use a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or a topical agents to remove

adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

Face, flexural and genital psoriasis

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

## **Secondary care management**

Phototherapy

- narrow band ultraviolet B light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

Systemic therapy

- oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- ciclosporin
- systemic retinoids
- biological agents: infliximab, etanercept and adalimumab
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials

Mechanism of action of commonly used drugs:

- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Question 5 of 73

You notice an abnormality on the neck of a 40-year-old woman:



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Which one of the following is most associated with this appearance?

[Lung cancer14%](#)[Acute pancreatitis9%](#)[Haemochromatosis11%](#)[Polycystic ovarian syndrome60%](#)[Digoxin use5%](#)

This patient has acanthosis nigricans which is associated with a number of hyperinsulinaemia states such as polycystic ovarian syndrome.

Whilst acanthosis nigricans can be associated with any type of cancer by far the most common malignant cause is gastrointestinal adenocarcinoma.

### **Acanthosis nigricans**

Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin

#### **Causes**

- gastrointestinal cancer
- diabetes mellitus
- obesity
- polycystic ovarian syndrome
- acromegaly
- Cushing's disease

- hypothyroidism
- familial
- Prader-Willi syndrome
- drugs: oral contraceptive pill, nicotinic acid



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Question 6 of 73

A 49-year-old woman complains of 'spots' on her cheeks. She has tried using her daughter's 'Clearasil' but this has had no effect.



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What is the most likely diagnosis?

[Seborrhoeic dermatitis8%](#)[Systemic lupus erythematosus7%](#)[Perioral dermatitis3%](#)[Late-onset acne vulgaris13%](#)[Acne rosacea69%](#)

Perioral dermatitis is a differential diagnosis but it does not commonly affect the cheeks.

## Acne rosacea

Acne rosacea is a chronic skin disease of unknown aetiology

### Features

- typically affects nose, cheeks and forehead
- flushing is often first symptom
- telangiectasia are common
- later develops into persistent erythema with papules and pustules
- rhinophyma

- ocular involvement: blepharitis

## Management

- topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques)
- more severe disease is treated with systemic antibiotics e.g. Oxytetracycline
- recommend daily application of a high-factor sunscreen
- camouflage creams may help conceal redness
- laser therapy may be appropriate for patients with prominent telangiectasia

## Question 8 of 73

A 45 year old man with mild learning difficulties and newly diagnosed advanced HIV (CD4 count 65 /mm<sup>3</sup>) attends A&E from his residential home. He has an intensely itchy rash on his hands, arms, groin, legs and feet. He was recently commenced on Atripla ( Emtricitabine, Tenofovir, Efavirenz) and co-trimoxazole.



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There is extensive crusted scaling on his arms, groins and hands. On closer examination there are grey burrow marks between the webs of his fingers and toes. There are itchy nodules extensively over the palms and backs of his hands.

What is the most appropriate treatment?



Isolate and apply topical malathion cream for 24 hours 41% Isolate and stop co-trimoxazole 5% Discharge with topical steroids 4% Change his antiretroviral therapy to a second line regimen 6% Isolate and give ivermectin orally 44%

## Scabies

Scabies is caused by the mite *Sarcoptes scabiei* and is spread by prolonged skin contact. It typically affects children and young adults.

The scabies mite burrows into the skin, laying its eggs in the stratum corneum. The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

### Features

- widespread pruritus
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
- in infants the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

### Management

- permethrin 5% is first-line
- malathion 0.5% is second-line
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

### Patient guidance on treatment (from Clinical Knowledge Summaries)

- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.



The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation. Patients should be given the following instructions:

- apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and leave on the skin for 8-12 hours for permethrin, or for 24 hours for malathion, before washing off
- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- repeat treatment 7 days later

### **Crusted (Norwegian) scabies**

Crusted scabies is seen in patients with suppressed immunity, especially HIV.



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The crusted skin will be teeming with hundreds of thousands of organisms.

Ivermectin is the treatment of choice and isolation is essential

#### **Question 1 of 65**

A 64-year-old man presents with a 'rash' on his legs which has developed over the past few days:



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He complains of feeling generally 'run-down' but review of systems is unremarkable. What is the most likely underlying cause?

[Vasculitis48%](#)[Erythema multiforme10%](#)[Necrotising fasciitis10%](#)[Kaposi sarcoma14%](#)[Venous eczema18%](#)

Kaposi sarcoma may cause similar skin changes to the larger lesions but would not typically cause petechiae.

Vasculitis is commonly limited to the skin and may be caused by infections, drugs, autoimmune disorders and malignancy.

## **Vasculitides**

Large vessel

- temporal arteritis

- Takayasu's arteritis

#### Medium vessel

- polyarteritis nodosa
- Kawasaki disease

#### Small vessel

- ANCA-associated vasculitides (Wegener's\*, Churg-Strauss\*, microscopic polyangiitis)
- Henoch-Schonlein purpura
- cryoglobulinaemic vasculitis

\*may also affect medium-sized vessels

#### Question 2 of 65

A 78-year-old man presents with a lesion on his right cheek. This has slowly been getting larger over the past 6-7 months. He has no history of skin problems and the only past medical history of note is osteoarthritis of the knee and depression.



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What is the most likely diagnosis?

[Amelanotic malignant melanoma 8% Basal cell carcinoma 26% Keratoacanthoma 5% Squamous cell carcinoma 56% Actinic keratosis 5%](#)

Don't be fooled into thinking this is a basal cell carcinoma (BCC) by the presence of telangiectasia near the lesion. With BCC's these are generally found on the rolled edges of the lesion rather than being scattered around the periphery.

### **Squamous cell carcinoma of the skin**

Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

### **Image gallery**



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## **Treatment**

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## **Prognosis**

### **Good Prognosis**

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### **Poor prognosis**

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason

### Question 3 of 65

A 24 year-old gentleman is referred for your opinion from the Emergency Department. He presented with his first tonic-clonic seizure. A CT scan of his head shows a contrast enhancing lesion in the left frontal lobe. On taking a history you elicit that he has been having recurrent nosebleeds and dark stools for the past 12 months.

What is the likely unifying diagnosis?

[Peutz Jeghers syndrome 11%](#) [Hereditary haemorrhagic telangiectasia 71%](#) [Tuberous sclerosis 8%](#) [Von Willebrand disease 5%](#) [Neurofibromatosis - type 2 6%](#)

This young gentleman is likely to have a diagnosis of hereditary haemorrhagic telangiectasia (HHT). The contrast enhancing lesion on the CT scan represents an arterio-venous malformation. The history of recurrent nosebleeds and melena is typical of HHT and are secondary to telangiectasia on the nasal and gastrointestinal mucosa.

### **Hereditary haemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)



- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



© Image used on license from [Radiopaedia](https://radiopaedia.org/)

The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

Question 5 of 65

A 52-year-old man asks you to look at the side of his tongue. The white patches have been present for the past few months and are asymptomatic. He is a smoker who is known to have type 2 diabetes mellitus.



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What is the most likely diagnosis?

[Candidiasis10%](#)[Squamous cell carcinoma6%](#)[Lichen sclerosus10%](#)[Oral leukoplakia68%](#)[Geographic tongue6%](#)

The asymptomatic and prolonged nature of the symptoms goes against a diagnosis of candidiasis. Lichen planus (rather than sclerosus) is a differential diagnosis but tends to have a slightly different appearance - typically a symmetrical white lace-like pattern on the buccal mucosa. Squamous cell carcinoma is not the most likely diagnosis as only around 1% of oral leukoplakias become malignant.

This patient should be referred for a biopsy to confirm the diagnosis.

## Leukoplakia

Leukoplakia is a premalignant condition which presents as white, hard spots on the mucous

membranes of the mouth. It is more common in smokers.

Leukoplakia is said to be a diagnosis of exclusion. Candidiasis and lichen planus should be considered, especially if the lesions can be 'rubbed off'

Biopsies are usually performed to exclude alternative diagnoses such as squamous cell carcinoma and regular follow-up is required to exclude malignant transformation to squamous cell carcinoma, which occurs in around 1% of patients.



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### Question 6 of 65

A 25-year-old Caucasian male presents with his first ever episode of witnessed generalised seizure, with witnessed jerking of his right arm and leg, lasting for 4 minutes terminated by benzodiazepines administered by paramedics. There is no other past medical history and documentation of head injuries. His past medical history includes recurrent epistaxes since childhood and current treatment for a left calf deep vein thrombosis provoked following two recent long-haul flights from Australia. A thrombophilia screen has subsequently been negative. Family history is unavailable.

On examination, the patient is confused postictally and is uncooperative with the examination. You note that his pupils are equal and reactive, he is moving all 4 limbs with no obvious focal neurology. There appears to be no visual or sensory neglect. A urinary toxicology screen is negative.

His blood tests and arterial blood gas are as follows:

Hb	175 g/l
MCV	87 fl
Platelets	$223 \times 10^9/l$
WBC	$9.2 \times 10^9/l$
Urea	6.6 mmol/l
Creatinine	64 $\mu\text{mol/l}$
CRP	24 mg/l

pH	7.32
PaO <sub>2</sub>	9.1 kPa
PaCO <sub>2</sub>	4.2 kPa
Lactate	4.2 mmol/l
Bicarbonate	16 mmol/l

With sedation, the patient undergoes a CT head, which demonstrates an arterio-venous fistula in his right parietal lobe.

The patient remains an inpatient while discussed for management with neurosurgeons and returns to baseline with no focal neurological deficits. At 48 hours after admission, he develops sudden onset left face, arm and leg weakness and loss of sensation, with flaccid tone, downgoing plantars. A repeat CT head confirms a right middle cerebral artery ischaemic stroke.

What is the unifying diagnosis?

[Malignancy of unclear primary3% Haemorrhagic hereditary telangiectasia67% Saddle pulmonary embolus5% Polycythaemia rubra vera15% Paroxysmal nocturnal haemoglobinuria10%](#)

This is a difficult question: the patient has an intracerebral arterio-venous fistula and likely at least another in his pulmonary vasculature, resulting in a chronic hypoxaemia (note normal bicarbonate and secondary polycythaemia), ruling out an acute pulmonary embolus and likely resulting in a paradoxical stroke. Primary polycythaemia rubra vera should not result in hypoxaemia. There does not appear to be an underlying prothrombotic element: his current DVT is uncommon but appears provoked with a negative thrombophilia. There is little to suggest malignancy.

A previous history of epistaxis is also suggestive of haemorrhagic hereditary telangiectasia (HHT), which appears to be the most common and earliest clinical feature. Diagnosis is clinched by the consensus Curacao criteria, requiring the following 4 features to be investigated in this case: spontaneous or recurrent epistaxis, multiple cutaneous telangiectasia (a full dermatological examination is essential), visceral involvement (in this case, pulmonary and cerebral AVMs) and a first-degree relative with HHT (family history is required). Meeting at least 3 features produces a definite diagnosis while 2 of 4 features suggests 'suspected' diagnosis.

### **Hereditary haemorrhagic telangiectasia**

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



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The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

#### Question 7 of 65

A 53-year-old man presents complaining of an itchy scalp and dandruff. On examination he is noted to have eczema on his scalp, behind his ears and around his nose.





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He has tried 'Head and Shoulders' and 'Neutrogen T-gel' but with poor results. Which one of the following is the most appropriate treatment for his scalp?

[Topical hydrocortisone 12%](#) [Topical dermivate 10%](#) [Topical selenium sulphide 17%](#) [Oral terbinafine 9%](#) [Topical ketoconazole 52%](#)

### **Seborrhoeic dermatitis in adults**

Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called *Malassezia furfur* (formerly known as *Pityrosporum ovale*). It is common, affecting around 2% of the general population

#### **Features**

- eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- otitis externa and blepharitis may develop

Associated conditions include



- HIV
- Parkinson's disease

#### Scalp disease management

- over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- the preferred second-line agent is ketoconazole
- selenium sulphide and topical corticosteroid may also be useful

#### Face and body management

- topical antifungals: e.g. Ketoconazole
- topical steroids: best used for short periods
- difficult to treat - recurrences are common

#### Question 8 of 65

You review a 31-year-old woman who has had Crohn's disease for the past 12 years. She is currently on infliximab therapy.



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What is the most likely diagnosis?

Pyoderma gangrenosum 66% Acute febrile neutrophilic dermatosis 11% Squamous cell carcinoma 6% Pyogenic granuloma 12% Behcet's disease 5%

## **Pyoderma gangrenosum**

### Features

- typically on the lower limbs
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

### Causes\*

- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

### Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

\*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes



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Question 9 of 65  
Please look at the image below:



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What is the most likely diagnosis?

[Plaque psoriasis](#)69%[Atopic eczema](#)6%[Bowen's disease](#)5%[Flexural psoriasis](#)16%[Tinea corporis](#)4%

## Psoriasis

Psoriasis is a common (prevalence around 2%) and chronic skin disorder. It generally presents with red, scaly patches on the skin although it is now recognised that patients with psoriasis are at increased risk of arthritis and cardiovascular disease.

### Pathophysiology

- multifactorial and not yet fully understood
- genetic: associated HLA-B13, -B17, and -Cw6. Strong concordance (70%) in identical twins
- immunological: abnormal T cell activity stimulates keratinocyte proliferation. There is increasing evidence this may be mediated by a novel group of T helper cells producing IL-17, designated Th17. These cells seem to be a third T-effector cell subset in addition to Th1 and Th2

- environmental: it is recognised that psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors

### Recognised subtypes of psoriasis

- plaque psoriasis: the most common sub-type resulting in the typical well demarcated red, scaly patches affecting the extensor surfaces, sacrum and scalp
- flexural psoriasis: in contrast to plaque psoriasis the skin is smooth
- guttate psoriasis: transient psoriatic rash frequently triggered by a streptococcal infection. Multiple red, teardrop lesions appear on the body
- pustular psoriasis: commonly occurs on the palms and soles



### Other features

- nail signs: pitting, onycholysis
- arthritis

### Complications

- psoriatic arthropathy (around 10%)
- increased incidence of metabolic syndrome
- increased incidence of cardiovascular disease
- increased incidence of venous thromboembolism
- psychological distress





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#### Question 1 of 55

A 24-year-old woman presents with new skin lesions.

She was the recipient of a renal transplant a year ago following IgA nephropathy. After several modifications to her immunosuppressive therapy, her graft function is stable with an eGFR of 80ml/min/1.73m<sup>2</sup>. She also has a past history of hypothyroidism for which she takes levothyroxine.

She had first noticed the lesions 3 months ago. She had noted them a few years previously but on that occasion, they had disappeared of their own accord. They are not itchy.

On examination she has well demarcated depigmented patches on her arm, her shoulders and her upper back; the lesions shine a yellow-green colour under Woods lamp.

What is the most likely diagnosis?

[Viteligo18%](#)[Pityriasis alba16%](#)[Idiopathic guttate hypomelanosis7%](#)[Pityriasis versicolor54%](#)[Seborrhoeic dermatitis5%](#)

The yellow-green fluorescence under Woods lamp is the key factor here; none of the other answers fluoresces in this way. Hence vitiligo is not correct and the history of hypothyroidism (an autoimmune illness that may be associated with vitiligo) is irrelevant. The description is not

consistent with seborrhoeic dermatitis, and the distribution of the rash is not consistent with either pityriasis alba or seborrhoeic dermatitis which typically affect the face.

## **Pityriasis versicolor**

Pityriasis versicolor, also called tinea versicolor, is a superficial cutaneous fungal infection caused by *Malassezia furfur* (formerly termed *Pityrosporum ovale*)

### Features

- most commonly affects trunk
- patches may be hypopigmented, pink or brown (hence versicolor). May be more noticeable following a suntan
- scale is common
- mild pruritus

### Predisposing factors

- occurs in healthy individuals
- immunosuppression
- malnutrition
- Cushing's

### Management

- topical antifungal. NICE Clinical Knowledge Summaries advise ketoconazole shampoo as this is more cost effective for large areas
- if extensive disease or failure to respond to topical treatment then consider oral itraconazole

### Question 2 of 55

A woman who is 24 weeks pregnant presents with a rash:





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What is the most likely diagnosis?

[Pityriasis rosea](#)4% [Pompholyx](#)5% [Primary herpes simplex infection](#)4% [Polymorphic eruption of pregnancy](#)25% [Pempfigoid gestationis](#)62%

The blistering lesions are clearly visible on this image.

### **Skin disorders associated with pregnancy**

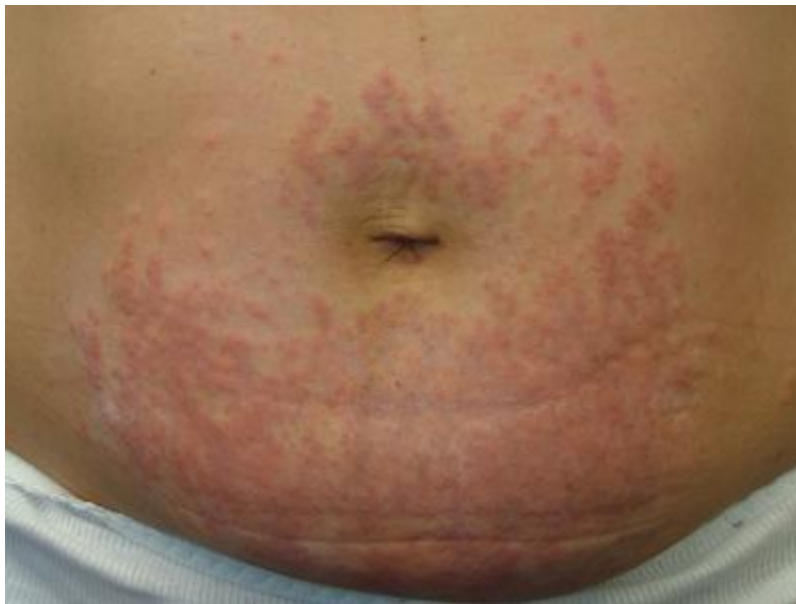
#### **Polymorphic eruption of pregnancy**

- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used



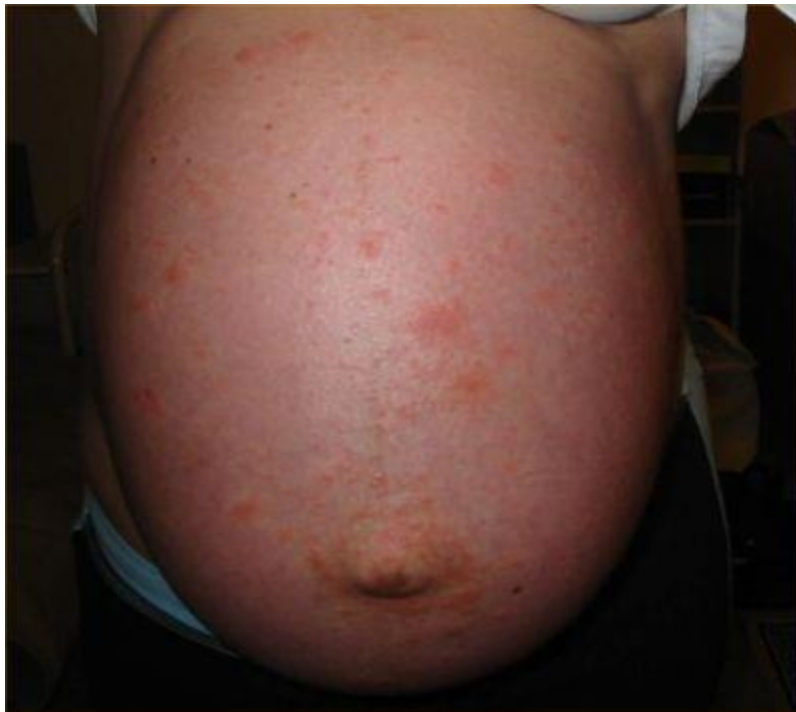
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Polymorphic eruption of pregnancy





## Polymorphic eruption of pregnancy



## Polymorphic eruption of pregnancy

### Pemphigoid gestationis

- pruritic blistering lesions
- often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
- usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- oral corticosteroids are usually required



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Pemphigoid gestationis



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Pemphigoid gestationis

Question 3 of 55

A 62-year-old woman presents with painful 'bruises' on her shins and forearms.



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She cannot remember knocking herself. What is the most likely diagnosis?

[Idiopathic thrombocytopenic purpura](#)5% [Erythema ab igne](#)5% [Thrombotic thrombocytopenic purpura](#)3% [Erythema nodosum](#)85% [Cellulitis](#)2%

## **Erythema nodosum**

### **Overview**

- inflammation of subcutaneous fat
- typically causes tender, erythematous, nodular lesions
- usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs)

- usually resolves within 6 weeks
- lesions heal without scarring

### Causes

- infection: streptococci, TB, brucellosis
- systemic disease: sarcoidosis, inflammatory bowel disease, Behcet's
- malignancy/lymphoma
- drugs: penicillins, sulphonamides, combined oral contraceptive pill
- pregnancy



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Question 4 of 52

A 47-year-old woman complains of an itchy neck and scalp:



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This skin condition is thought to occur as a result of a reaction to:

[Trichophyton rubrum19%](#) [Trichophyton schoenleinii13%](#) [Microsporum audouinii7%](#) [Candida albicans6%](#) [Malassezia furfur56%](#)

### **Seborrhoeic dermatitis in adults**

Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called *Malassezia furfur* (formerly known as *Pityrosporum ovale*). It is common, affecting around 2% of the general population

#### **Features**

- eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- otitis externa and blepharitis may develop

Associated conditions include

- HIV



- Parkinson's disease

#### Scalp disease management

- over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- the preferred second-line agent is ketoconazole
- selenium sulphide and topical corticosteroid may also be useful

#### Face and body management

- topical antifungals: e.g. Ketoconazole
- topical steroids: best used for short periods
- difficult to treat - recurrences are common

#### Question 7 of 52

A 23-year-old man presents as he is concerned about recent hair loss. Examination reveals the following:



What is the most likely diagnosis?

Telogen effluvium7%Alopecia areata69%Tinea capitis14%Male-pattern baldness4%Discoid lupus erythematosus6%

## **Alopecia areata**

Alopecia areata is a presumed autoimmune condition causing localised, well demarcated patches of hair loss. At the edge of the hair loss, there may be small, broken 'exclamation mark' hairs

Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually. Careful explanation is therefore sufficient in many patients. Other treatment options include:

- topical or intralesional corticosteroids
- topical minoxidil
- phototherapy
- dithranol
- contact immunotherapy
- wigs

Question 8 of 52

A woman who is 30 weeks pregnant asks you about an itchy rash on her abdomen:



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What is the most likely diagnosis?

[Pre-eclampsia 5%](#) [Polymorphic eruption of pregnancy 65%](#) [Primary herpes simplex infection 5%](#) [Pemphigoid gestationis 18%](#) [Pompholyx 7%](#)

### **Skin disorders associated with pregnancy**

#### **Polymorphic eruption of pregnancy**

- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used



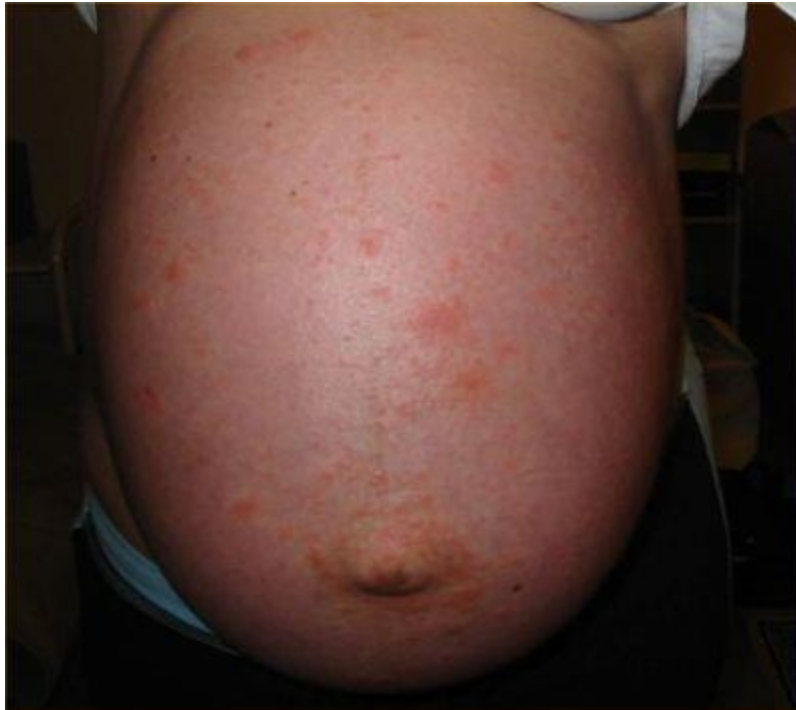
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Polymorphic eruption of pregnancy





## Polymorphic eruption of pregnancy



## Polymorphic eruption of pregnancy

### Pemphigoid gestationis

- pruritic blistering lesions
- often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
- usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- oral corticosteroids are usually required



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Pemphigoid gestationis



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Pemphigoid gestationis

Question 9 of 52  
Please look at the image below:



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The lesion has been getting bigger for the past few weeks. There is no history of trauma. What is the most likely diagnosis?

[Basal cell carcinoma](#)9%[Seborrhoeic keratosis](#)8%[Bowen's disease](#)57%[Tinea corporis](#)7%[Nummular eczema](#)18%

## **Bowen's disease**

Bowen's disease is a type of intraepidermal squamous cell carcinoma. More common in elderly females. There is around a 3% chance of developing invasive skin cancer

### Features

- red, scaly patches
- often occur on sun-exposed areas such as the lower limbs

### Management options:

- topical 5-fluorouracil or imiquimod
- cryotherapy



- excision



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Question 13 of 52

A 34-year-old woman presents with a rash on her face. She has been feeling generally unwell for around three months with lethargy and has a variety of joint pains



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What is the most likely diagnosis?

[Impetigo3%](#) [Perioral dermatitis4%](#) [Sarcoidosis4%](#) [Acne rosacea9%](#) [Systemic lupus erythematosus80%](#)

### **Skin disorders associated with SLE**

Skin manifestations of systemic lupus erythematosus (SLE)

- photosensitive 'butterfly' rash
- discoid lupus
- alopecia
- livedo reticularis: net-like rash



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Note the nasolabial sparing of the malar rash from this woman who has SLE



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Note how this image of cutaneous SLE is slightly atypical as it does not have the characteristic nasolabial sparing

Question 14 of 52

A 38-year-old man presents with a sudden onset rash. He is otherwise well in himself and has no notable past medical history. You see from his notes he has had a recent tonsillitis for which he

received amoxicillin. On examination, there are multiple papules on his trunk and proximal extremities. There is a fine scale on several of these lesions. What is the most likely diagnosis?

[Drug eruption22% Pityriasis rosea13% Nummular dermatitis7% Guttate psoriasis51% Treponema pallidum6%](#)

Guttate psoriasis usually presents in children and adults younger than 30 years of age. It can occur as the first presentation of psoriasis or as an acute exacerbation of plaque psoriasis, particularly after acute streptococcal infection (usually of the throat) or viral infection.

Lesions are small, round or oval (2 mm to 1 cm in diameter) scaly papules. They may be pink or red, but this can vary depending on the person's skin colour. Lesions occur all over the body, usually in large numbers and particularly on the trunk and proximal limbs (although the distal limbs can also be involved). Guttate psoriasis can occur on the face, ears, and scalp, but is rarely seen on the soles of the feet.

### **Psoriasis: guttate**

Guttate psoriasis is more common in children and adolescents. It may be precipitated by a streptococcal infection 2-4 weeks prior to the lesions appearing

#### **Features**

- tear drop papules on the trunk and limbs



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## Management

- most cases resolve spontaneously within 2-3 months
- there is no firm evidence to support the use of antibiotics to eradicate streptococcal infection
- topical agents as per psoriasis
- UVB phototherapy
- tonsillectomy may be necessary with recurrent episodes

## Differentiating guttate psoriasis and pityriasis rosea

	Guttate psoriasis	Pityriasis rosea
<b>Prodrome</b>	Classically preceded by a streptococcal sore throat 2-4 weeks	Many patients report recent respiratory tract infections but this is not common in questions
<b>Appearance</b>	'Tear drop', scaly papules on the trunk and limbs	Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions.  May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
<b>Treatment / natural history</b>	Most cases resolve spontaneously within 2-3 months Topical agents as per psoriasis UVB phototherapy	Self-limiting, resolves after around 6 weeks

Question 15 of 52

A 78-year-old woman presents with a number of blistering lesions on her torso. Around one week prior to the skin lesions developing she noticed widespread mouth ulceration:





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What is the most likely diagnosis?

[Epidermolysis bullosa](#)6%[Pemphigus vulgaris](#)61%[Bullous pemphigoid](#)13%[Stevens-Johnson Syndrome](#)14%[Staphylococcal scalded skin syndrome](#)6%

### **Pemphigus vulgaris**

Pemphigus vulgaris is an autoimmune disease caused by antibodies directed against desmoglein 3, a cadherin-type epithelial cell adhesion molecule. It is more common in the Ashkenazi Jewish population

## Features

- mucosal ulceration is common and often the presenting symptom. Oral involvement is seen in 50-70% of patients
- skin blistering - flaccid, easily ruptured vesicles and bullae. Lesions are typically painful but not itchy. These may develop months after the initial mucosal symptoms. Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin
- acantholysis on biopsy



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Mucosal ulceration is common with pemphigus





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## Management

- steroids
- immunosuppressants

## Question 16 of 52

A 33-year-old woman asks you to look at a 'spot' on her arm that has been present for several months. It has not changed recently and is completely asymptomatic.



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What is the most likely diagnosis?

[Leiomyoma10%](#)[Basal cell carcinoma11%](#)[Amelanotic malignant melanoma9%](#)[Dermatofibroma51%](#)[Nodular prurigo18%](#)

## Dermatofibroma

Dermatofibromas (also known as histiocytomas) are common benign fibrous skin lesions. They are caused by the abnormal growth of dermal dendritic histiocyte cells, often following a precipitating injury. Common areas include the arms and legs.

## Image gallery



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This image shows the 'pinch test'. A dimple is formed when a dermatofibroma is pinched indicating tethering of the skin to the underlying fibrous tissue

#### Question 18 of 52

A 72-year-old woman presents with a new skin marking. She has noticed it recently and is fairly sure it was not present six months ago. It has not caused her any symptoms and has not been itching. On examination, it is a raised, slightly ulcerated, 7mm diameter lesion on her chest. What clinical finding would make squamous cell carcinoma more likely than basal cell carcinoma?

[Telangiectasia16%](#) [Not associated with ulceration14%](#) [Pearly appearance8%](#) [Erythematous base42%](#) [Nodular edge20%](#)

The correct answer is erythematous base. Squamous cell cancers present as crusty enlarging lumps on a background of actinic keratosis on sun-exposed skin. They may ulcerate and are often tender or painful. Basal cell cancers usually have telangiectasia, pearly appearance and have a nodular edge.

#### **Squamous cell carcinoma of the skin**



Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

### Image gallery



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## Treatment

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## Prognosis

### Good Prognosis

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### Poor prognosis

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason

Question 1 of 34

A 56-year-old woman develops a rash in both axilla:



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What is the most likely diagnosis?

[Pellagra5%](#)[Erythema gyratum repens5%](#)[Hidradenitis suppurativa6%](#)[Tinea corporis6%](#)[Acanthosis nigricans78%](#)

This image shows the typical brown, velvety patches which affect the axilla, neck and groin.

### **Acanthosis nigricans**

Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin

Causes

- gastrointestinal cancer
- diabetes mellitus
- obesity
- polycystic ovarian syndrome
- acromegaly
- Cushing's disease
- hypothyroidism
- familial
- Prader-Willi syndrome

- drugs: oral contraceptive pill, nicotinic acid



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### Question 3 of 34

A 73-year-old woman attended dermatology clinic for review of a skin lesion on her right cheek. The patient had recently returned to the United Kingdom having been resident in southern Spain for the previous 20 years. She described the development of a lump just under her right eye over approximately the past six months. She also recalled having a area of slightly dry and sore skin in a similar location prior to the emergence of the lesion, although she had not sought medical attention for this. The patient denied having any symptoms from the lesion, although was very concerned and upset about the unsightly appearance it caused.

The patient's medical history included rheumatoid arthritis, type 2 diabetes mellitus, hypertension and intermittent episodes of gout. She had no previous dermatological condition. Her regular medications were methotrexate 15 mg weekly, metformin 1000 mg twice daily, ramipril 2.5 mg daily and naproxen 500 mg as required. She denied any previous treatments for cancer.

Examination of the patient demonstrated an approximately spherical nodule 11 mm in diameter arising from the patient's cheek 15 mm inferior to her eyelid. Crusting was noted on the surface of the nodule, but there was no hyperkeratosis, induration or ulceration.

A biopsy of the lesion is taken during clinic assessment with histology demonstrating squamous cell carcinoma.

What is the appropriate technique for treatment of the patient's lesion?

[Electrodessiccation5% Wide local excision with 4 mm margin of normal skin30% Mohs micrographic surgery43% Wide local excision with 6 mm margin of normal skin18% Radiotherapy5%](#)

The patient has a facial cutaneous squamous cell carcinoma in a functionally and cosmetically important region. Her history of immunosuppression with methotrexate could also lead to the tumour being considered high risk, although the increased risk of squamous cell carcinoma is most well characterised in those individuals highly immunosuppressed to prevent transplant rejection.

Mohs micrographic surgery is a specialised technique reserved for use in high risk tumours or those in functionally or cosmetically important areas. The technique involves histological examination of the tumour during the procedure to ensure adequate margins and complete tumour clearance. The technique provides a high cure rate and maximum tissue conservation.

In less sensitive areas of the body, wide local excision is the treatment of choice. Low risk tumours with diameter < 2 mm require margins of 4 mm, with 6 mm margins being required in high-risk or larger tumours.

Radiotherapy is an alternative treatment option for individuals not suitable for surgery but has a higher recurrence rate than surgical excision. Electrodesiccation (curettage and cautery) is occasionally used for low risk cutaneous squamous cell carcinomas on the extremities or trunk.

Aslam A, Patel A. Facial cutaneous squamous cell carcinoma. BMJ 2016;352:i1513.

## **Squamous cell carcinoma of the skin**

Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

## **Image gallery**



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## Treatment

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## Prognosis

### Good Prognosis

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### Poor prognosis

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason



Question 4 of 34

A 19-year-old woman asks you to have a look at a 'tag' on her neck. It developed around two months ago and has bled on a number of occasions after catching it.



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What is the most likely diagnosis?

[Pyogenic granuloma55%](#) [Capillary haemangioma28%](#) [Vital wart6%](#) [Malignant melanoma4%](#) [Molluscum contagiosum6%](#)

### **Pyogenic granuloma**

Pyogenic granuloma is a relatively common benign skin lesion. The name is confusing as they are neither true granulomas nor pyogenic in nature. There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.

The cause of pyogenic granuloma is not known but a number of factors are linked:

- trauma
- pregnancy
- more common in women and young adults

### Features

- most common sites are head/neck, upper trunk and hands. Lesions in the oral mucosa are common in pregnancy
- initially small red/brown spot
- rapidly progress within days to weeks forming raised, red/brown lesions which are often spherical in shape
- the lesions may bleed profusely or ulcerate

### Management

- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist. Removal methods include curettage and cauterisation, cryotherapy, excision



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#### Question 5 of 34

A 34-year-old man presents with a scaly rash on his elbows and knees that has been getting progressively worse for the past 3 months. He has tried using some of his wife's Diprobase cream which has helped the itching somewhat.



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Following NICE guidance, what is the most appropriate next step in management?

[Topical potent corticosteroid + vitamin D analogue](#)63% [Topical potent corticosteroid](#)14% [Refer for ultraviolet light therapy](#)4% [Topical vitamin D analogue](#)13% [Topical coal tar](#)6%

Topical potent corticosteroid + vitamin D analogue is first-line for chronic plaque psoriasis

## Psoriasis: management

NICE released guidelines in 2012 on the management of psoriasis and psoriatic arthropathy. Please see the link for more details.

Management of chronic plaque psoriasis

- regular emollients may help to reduce scale loss and reduce pruritus
- first-line: NICE recommend a potent corticosteroid applied once daily plus vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- second-line: if no improvement after 8 weeks then offer a vitamin D analogue twice daily
- third-line: if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a coal tar preparation applied once or twice daily
- short-acting dithranol can also be used



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### Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms



- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g. > 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

What should I know about vitamin D analogues?

- examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



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A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

### Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

### Scalp psoriasis

- NICE recommend the use of potent topical corticosteroids used once daily for 4 weeks
- if no improvement after 4 weeks then either use a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or a topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

### Face, flexural and genital psoriasis

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

## Secondary care management

### Phototherapy

- narrow band ultraviolet B light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

### Systemic therapy

- oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- ciclosporin
- systemic retinoids



- biological agents: infliximab, etanercept and adalimumab
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials

Mechanism of action of commonly used drugs:

- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Question 7 of 34

A 50-year-old man who has had a cough for the past week develops a rash. It initially appeared on his arms but has now spread to the torso:



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What is the most likely underlying diagnosis?

[Goodpasture's syndrome](#)5% [Adenovirus](#)10% [Mycoplasma pneumoniae](#)73% [Legionella pneumophila](#)5% [Rhinovirus](#)7%

This patient has developed erythema multiforme (EM), a known complication of Mycoplasma infection. *Mycoplasma pneumoniae* is the second most common trigger of EM after the herpes simplex virus.

## Erythema multiforme

Erythema multiforme is a hypersensitivity reaction which is most commonly triggered by infections. It may be divided into minor and major forms.

Previously it was thought that Stevens-Johnson syndrome (SJS) was a severe form of erythema multiforme. They are now however considered as separate entities.

### Features

- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild

### Causes

- viruses: herpes simplex virus (the most common cause), Orf\*
- idiopathic
- bacteria: *Mycoplasma*, *Streptococcus*
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus
- sarcoidosis
- malignancy



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### **Erythema multiforme major**

The more severe form, erythema multiforme major is associated with mucosal involvement.



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Example of mucosal involvement in erythema multiforme major

\*Orf is a skin disease of sheep and goats caused by a parapox virus

Question 1 of 26

A 60-year-old man asks you to have a look at a 'sore' on his right ear.



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It has been present for around 6 months and is not painful. What is the most likely diagnosis?

[Fungal otitis externa](#)5%[Actinic keratosis](#)35%[Pyogenic granuloma](#)6%[Basal cell carcinoma](#)10%[Chondrodermatitis nodularis helices](#)44%

Chondrodermatitis nodularis helices is usually painful.

### Actinic keratoses

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

#### Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present



Management options include

- prevention of further risk: e.g. sun avoidance, sun cream
- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

Question 5 of 26

A 45 year-old woman presents to her GP with an ulcer on her left shin. It has been present for the past 4 months and gradually got bigger. It is tender and yellow-brown in colour and there appears to be another smaller lesion that is growing next to the bigger one. She has a past medical history of multiple sclerosis, of which she is currently in remission phase and type 1 diabetes mellitus. Her only regular medication includes insulin.

What is the most appropriate treatment?

[Flucloxacillin10%](#) [Topical corticosteroids36%](#) [TED stockings11%](#) [Oral corticosteroids28%](#) [Topical tacrolimus14%](#)

The most likely diagnosis is necrobiosis lipoidica, a rare granulomatous skin disorder which can affect the shin of insulin dependent diabetics. Skin biopsy can confirm the diagnosis, although it is often done clinically and topical steroids are a useful treatment, along with injectable corticosteroids and camouflage creams.

## **Shin lesions**

The differential diagnosis of shin lesions includes the following conditions:

- erythema nodosum
- pretibial myxoedema
- pyoderma gangrenosum

- necrobiosis lipoidica diabetorum

Below are the characteristic features:

#### Erythema nodosum

- symmetrical, erythematous, tender, nodules which heal without scarring
- most common causes are streptococcal infections, sarcoidosis, inflammatory bowel disease and drugs (penicillins, sulphonamides, oral contraceptive pill)

#### Pretibial myxoedema

- symmetrical, erythematous lesions seen in Graves' disease
- shiny, orange peel skin

#### Pyoderma gangrenosum

- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- idiopathic in 50%, may also be seen in inflammatory bowel disease, connective tissue disorders and myeloproliferative disorders

#### Necrobiosis lipoidica diabetorum

- shiny, painless areas of yellow/red skin typically on the shin of diabetics
- often associated with telangiectasia

#### Question 6 of 26

A 65-year-old man presents after developing an intensely itchy 'rash' on the dorsum of his left hand. This has now been present for around 6 weeks. He also points out a similar lesion on the dorsum of the right wrist which has appeared in the past week. His past medical history includes type 2 diabetes mellitus and depression. From reviewing his medication history it seems that citalopram has recently been changed to sertraline around 8 weeks ago due to a poor response. The lesion is shown below:





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What is the most likely diagnosis?

[Discoid eczema 66%](#) [Contact dermatitis 7%](#) [Psoriasis 7%](#) [Allergic reaction to sertaline 10%](#) [Lichen planus 10%](#)

This lesion is typical of discoid eczema. Lesions are typically well defined, intensely pruritic and located on the peripheries. Discoid, or nummular, eczema shows a bimodal distribution, being more common in the 20's (predominately females) and the 60's (predominately males).

These lesions are not consistent with an allergic reaction. If the option of a fixed drug eruption had been given the differential would have been much harder as the appearance is much more similar. Fixed drug eruptions however tend to occur within 24 hours of starting the drug and disappear after 10 days.

The location of the lesions is not consistent with contact dermatitis.

## **Discoid eczema**

Discoid eczema is sometimes referred to as nummular eczema, meaning coin-shaped.

## Features

- typically present as round or oval plaques on the extremities
- the lesions are extremely itchy
- central clearing may occur giving a similar appearance to tinea corporis



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Image showing discoid eczema

## Question 7 of 26

A 30-year-old cleaner presents with a four-week history of recurrent vesicular lesions on her hands. She describes these lesions as initially appearing on the sides of her fingers before progressing to more generalised vesicles on her palms. They then break down and become intensely itchy, dry and cracked. She has tried using over the counter moisturisers but these have not helped.

She finds that the cleaning products she works with makes the rash worse and has been wearing rubber gloves to try and avoid this happening. She has also taken the past two weeks off work due to the cracked and inflamed skin on her hands.

She has no past medical history of note but does describe an allergy to nickel at the age of 14 around the time of her first ear piercings.

She currently takes the oral contraceptive pill.

On examination, you find linear 1-2mm vesicles along most of her digits with evidence of lichenification, cracking and inflamed skin. There is no evidence of any other skin rash

elsewhere.

What is the most likely diagnosis?

[Digital Herpes Simplex5% Irritant contact dermatitis41% Pompholyx29% Pustular psoriasis6% Allergic contact dermatitis19%](#)

This is a classic history of pompholyx eczema. It typically affects the hands (80% of the time) or the feet (12%), or both and presents with small vesicles along the digits and palms/soles. These then de-roof causing intense itching and drying of the skin.

Pompholyx eczema has been associated with a nickel allergy.

The other answers can also present with vesicular eruptions on the hands but the clinical presentations are different.

Herpetic whitlow would lead to a painful outcrop of vesicles and would be unlikely to cause lesions at multiple sites in an immunocompetent person.

Pustular psoriasis is an acute form of psoriasis which leads to widespread pustules with systemic upset.

Irritant and allergic contact dermatitis can present similarly to pompholyx eczema but are as a result of contact with an irritant or allergen. As a cleaner and with a nickel allergy she could be susceptible to both these conditions. However the fact that she has been wearing rubber gloves and has removed herself from potential contacts suggests that a specific chemical is unlikely to be the cause of her symptoms.

## **Pompholyx**

Pompholyx is a type of eczema which affects both the hands (cheiropompholyx) and the feet (pedopompholyx). It is also known as dyshidrotic eczema

### **Features**

- small blisters on the palms and soles
- pruritic, sometimes burning sensation
- once blisters burst skin may become dry and crack

## Management

- cool compresses
- emollients
- topical steroids



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Image showing discoid eczema

### Question 8 of 26

A 92-year-old attends dermatology clinic with her daughter. The patient had initially been seen four weeks previously with a skin lesion on her right shoulder. A biopsy of the lesion had been taken at the initial appointment and histology demonstrated the lesion to be a cutaneous squamous cell carcinoma.

The patient had an extensive past-medical history including atrial fibrillation, severe left ventricular systolic dysfunction, chronic renal failure, fractured neck of femur and gout. Her regular medications were bumetanide 2 mg twice daily, ramipril 1.25 mg daily, bisoprolol 2.5 mg daily, spironolactone 25 mg daily, allopurinol 300 mg daily, denosumab 60 mg every six months and warfarin (target INR 2.0-3.0). The patient lived with her daughter and required

assistance with all activities of daily living. Her mobility was limited to a few meters with the use of a walking frame.

Examination of the patient's right shoulder demonstrated a well defined crusted nodule with a diameter of approximately 10 mm.

While concerned by the lesion on her shoulder, the patient was very reluctant to undergo any invasive surgical procedure. In particular, she stated that the surgery she had required to treat her fractured hip had been extremely traumatic. The patient's daughter was in agreement with her point of view but asked if an alternative treatment technique could be considered.

Histology from skin biopsy: well differentiated squamous cell carcinoma

What is the most appropriate treatment option for this patient's cutaneous squamous cell carcinoma?

[Photodynamic therapy6%Radiotherapy27%Mohs micrographic surgery31%Cryotherapy17%Topical treatment with fluorouracil19%](#)

The patient has a well defined and well differentiated primary cutaneous squamous cell carcinoma. Her reluctance to undergo surgery and multiple co-morbidities mean that wide local excision (the usual treatment of choice) would not be appropriate.

Of the available options, radiotherapy is the most appropriate next line treatment. Radiotherapy can be used to treat small and well-defined lesions in patient not suitable for surgery. Outcomes are inferior to surgery with higher recurrence rates.

Mohs micrographic surgery is a technique whereby pathological specimens are examined during surgery to achieve complete tumour clearance with maximum tissue conservation. This specialist technique is reserved for high risk cutaneous squamous cell carcinomas and tumours in functionally and cosmetically sensitive sites.

The other possible answers are all treatment options for actinic keratosis and cutaneous squamous cell carcinoma in situ. There is no evidence for their use in cutaneous squamous cell carcinoma.

Aslam A, Patel A. Facial cutaneous squamous cell carcinoma. BMJ 2016;352:i1513.

## **Squamous cell carcinoma of the skin**

Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

### Image gallery



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## Treatment

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## Prognosis

### Good Prognosis

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### Poor prognosis

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason

## Question 9 of 26

A 43-year-old man presents with a three week history of an itchy rash on the flexor surfaces of his arms. He is generally fit and well and has no history of skin problems.



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What is the most likely diagnosis?

[Morphea8%](#) [Lichen sclerosus9%](#) [Lichen planus67%](#) [Psoriasis10%](#) [Idiopathic urticaria6%](#)

## **Lichen planus**

Lichen planus is a skin disorder of unknown aetiology, most probably being immune mediated.

### Features

- itchy, papular rash most common on the palms, soles, genitalia and flexor surfaces of arms
- rash often polygonal in shape, 'white-lace' pattern on the surface (Wickham's striae)
- Koebner phenomenon may be seen (new skin lesions appearing at the site of trauma)
- oral involvement in around 50% of patients
- nails: thinning of nail plate, longitudinal ridging



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Lichenoid drug eruptions - causes:

- gold
- quinine
- thiazides

Management

- topical steroids are the mainstay of treatment
- extensive lichen planus may require oral steroids or immunosuppression



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Image showing discoid eczema

Management is similar to normal eczema, although co-existent bacterial infection is common and may require treatment.

Question 11 of 26

A 34-year-old man who is known to have HIV presents with a non-itchy skin eruption on his lower abdomen. He feels otherwise well and has had no similar 'rashes' previously.



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What is the most likely diagnosis?

[Molluscum contagiosum](#)84%[Lichen planus](#)3%[Keratosis pilaris](#)3%[Kaposi sarcoma](#)7%[Seborrhoeic dermatitis](#)3%

## **Molluscum contagiosum**

Molluscum contagiosum is a common skin infection caused by molluscum contagiosum virus (MCV), a member of the Poxviridae family. Transmission occurs directly by close personal contact, or indirectly via fomites (contaminated surfaces) such as shared towels and flannels. The majority of cases occur in children (often in children with atopic eczema), with the maximum incidence in preschool children aged 1-4 years.

Typically, molluscum contagiosum presents with characteristic pinkish or pearly white papules

with a central umbilication, which are up to 5 mm in diameter. Lesions appear in clusters in areas anywhere on the body (except the palms of the hands and the soles of the feet). In children, lesions are commonly seen on the trunk and in flexures, but anogenital lesions may also occur. In adults, sexual contact may lead to lesions developing on the genitalia, pubis, thighs, and lower abdomen. Rarely, lesions can occur on the oral mucosa and on the eyelids.

Self care advice:

- Reassure people that molluscum contagiosum is a self-limiting condition.
- Spontaneous resolution usually occurs within 18 months
- Explain that lesions are contagious, and it is sensible to avoid sharing towels, clothing, and baths with uninfected people (e.g. siblings)
- Encourage people not to scratch the lesions. If it is problematic, consider treatment to alleviate the itch
- Exclusion from school, gym, or swimming is not necessary

Treatment is not usually recommended. If lesions are troublesome or considered unsightly, use simple trauma or cryotherapy, depending on the parents' wishes and the child's age:

- Squeezing (with fingernails) or piercing (orange stick) lesions may be tried, following a bath. Treatment should be limited to a few lesions at one time
- Cryotherapy may be used in older children or adults, if the healthcare professional is experienced in the procedure
- Eczema or inflammation can develop around lesions prior to resolution. Treatment may be required if:
  - Itching is problematic; prescribe an emollient and a mild topical corticosteroid (e.g. hydrocortisone 1%)
  - The skin looks infected (e.g. oedema, crusting); prescribe a topical antibiotic (e.g. fusidic acid 2%)

Referral may be necessary in some circumstances:

- For people who are HIV-positive with extensive lesions urgent referral to a HIV specialist
- For people with eyelid-margin or ocular lesions and associated red eye urgent referral to an ophthalmologist
- Adults with anogenital lesions should be referred to genito-urinary medicine, for screening for other sexually transmitted infections



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### Question 12 of 26

You review an 82-year-old woman who has developed 'sores' on her legs. For the past two years she has had dry, itchy skin around her ankles but over the past few weeks the skin has started to break down.





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What is the most likely diagnosis?

[Necrobiosis lipoidica diabetorum](#)23%[Pyoderma gangrenosum](#)18%[Arterial ulcers](#)11%[Venous ulcers](#)44%[Pretibial myxoedema](#)5%

The dry, skin represents varicose eczema. Arterial ulcers tend to have a more 'punched-out' appearance.

## **Venous ulceration**

Venous ulceration is typically seen above the medial malleolus

Investigations



- ankle-brachial pressure index (ABPI) is important in non-healing ulcers to assess for poor arterial flow which could impair healing
- a 'normal' ABPI may be regarded as between 0.9 - 1.2. Values below 0.9 indicate arterial disease. Interestingly, values above 1.3 may also indicate arterial disease, in the form of false-negative results secondary to arterial calcification (e.g. In diabetics)

## Management

- compression bandaging, usually four layer (only treatment shown to be of real benefit)
- oral pentoxifylline, a peripheral vasodilator, improves healing rate
- small evidence base supporting use of flavinoids
- little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression

## Question 13 of 26

A 72-year-old gentleman presents with a peeling and erythematous rash on both of his hands. He has noticed slight tingling in the same area but denies pain. He has a past medical history of colorectal cancer which was managed surgically with an anterior resection. He developed local recurrence of his cancer five months post-operatively. He is now on palliative chemotherapy with capecitabine and oxaliplatin every two weeks in order to control progression. His last treatment was one week ago. He has a history of type two diabetes mellitus, depression and has had a cholecystectomy when he was younger. On examination he appears frail and cachectic, but systemically well. His hands are shown to have patchy palmar erythema with mild desquamation. A similar rash is present on the soles of his feet.

Observations:

Saturations 97%

Respiratory rate 17/min

Blood pressure 132/73mmHg

Heart rate 71/min

Temperature 37.3°C

What is the most likely diagnosis?

[Erythromelalgia8%](#) [Palmoplantar psoriasis8%](#) [Palmar-plantar erythrodysesthesia69%](#) [Paraneoplastic syndrome12%](#) [Cellulitis4%](#)

The answer is palmar-planter erythrodysesthesia. The distribution of a dysesthetic erythematous

rash with desquamation of the palms and soles is a classic description of palmar-plantar erythrodysesthesia during chemotherapy. Cellulitis, paraneoplastic syndromes, and erythromelalgia do not fit this distribution, and palmoplantar psoriasis is associated with itching.

### **Palmar-plantar erythrodysesthesia**

Palmar-plantar erythrodysesthesia is a common side effect of many chemotherapy treatments, occurring from days to months into treatment. It usually presents with tingling or numbness first in the fingers and palms and then toes and soles of the feet. This is then followed by an erythematous rash which can desquamate, blister and ulcerate which can be associated with onycholysis. Management depends on severity; mild reactions with only dysesthesia and no pain can be managed with supportive care, but severe reactions with serious desquamation, blistering and ulceration will need to have treatment delayed and the dose of chemotherapy reduced.

Source:

Moos, Roger Von, Beat J.k. Thuerlimann, Matti Aapro, Daniel Rayson, Karen Harrold, Jalid Sehouli, Florian Scotte, Domenica Lorusso, Reinhard Dummer, Mario E. Lacouture, Jürgen Lademann, and Axel Hauschild. 'Pegylated Liposomal Doxorubicin-associated Handfoot Syndrome: Recommendations of an International Panel of Experts.' *European Journal of Cancer* 44.6 (2008): 781-90.

Question 14 of 26

A 78-year-old woman presents with a raised skin lesion on her face:



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What is the most likely diagnosis?

[Keratoacanthoma](#)15% [Basal cell carcinoma](#)47% [Actinic keratosis](#)15% [Squamous cell carcinoma](#)17% [Malignant melanoma](#)6%

## Basal cell carcinoma

Basal cell carcinoma (BCC) is one of the three main types of skin cancer. Lesions are also known as rodent ulcers and are characterised by slow-growth and local invasion. Metastases are extremely rare. BCC is the most common type of cancer in the Western world.

### Features

- many types of BCC are described. The most common type is nodular BCC, which is described here
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia
- may later ulcerate leaving a central 'crater'

Management options:

- surgical removal
- curettage
- cryotherapy
- topical cream: imiquimod, fluorouracil
- radiotherapy



Question 15 of 26

The lesion below started as a small red papule which grew in size before starting to ulcerate:



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Which one of the following conditions is most associated with this skin condition?

[Rheumatoid arthritis](#)50%[Sarcoidosis](#)24%[Primary herpes simplex virus infection](#)7%[Tuberculosis](#)11%[Thyrotoxicosis](#)9%

## **Pyoderma gangrenosum**

### Features

- typically on the lower limbs
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

### Causes\*

- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias

- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

### Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

\*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes



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#### Question 16 of 26

A 28-year-old man attends dermatology clinic for review after a referral from his GP. The patient reported a one-year history of uncomfortable and unsightly skin changes to the glans of his penis. The patient was unable to recall the exact onset of his symptoms, stated that the problem had gradually progressed from a minor inconvenience to the current situation when he felt his quality of life was being severely impacted. The most concerning symptom was persistent itch

associated with the glans of the patient's penis. In addition, the patient reported a recurrent red rash associated with the same area.

The patient reported that after the symptoms had started he had kept to a regime of regular application of over-the-counter moisturiser to prevent the area from becoming too dry. Having read about the problems sometimes associated with an excessive frequency of washing the genital area he only showered once per day, using a 'mild' soap. Prior to attendance at clinic, the patient's GP had tried a short course of topical hydrocortisone cream without significant benefit but had been reluctant to prescribe stronger topical corticosteroids. The patient stated that he did not have any rashes elsewhere on his body, or any prior history of dermatological conditions.

Following direct questions, the patient divulged his condition sometimes made sex uncomfortable but not painful. He regularly used condoms as a method of contraception and had been doing so for approximately the previous 10 years without any concerns. When his current issues had started he had attended a sexual health clinic with testing not revealing any evidence of sexually transmitted disease. The patient denied any urinary symptoms or erectile dysfunction.

The patient had a past medical history of asthma as a child that had resolved as he entered adulthood, with his father and younger brother both also suffering from asthma. He took no prescribed or over-the-counter medications and had no known drug allergies. The patient worked as a trainee accountant and smoked 10 cigarettes per day.

Examination of the patient's penis demonstrated an erythematous, scaly rash associated with the glans of the patient's penis. The patient was uncircumcised with the foreskin retracting easily and without discomfort. Examination of the patient's genital area was otherwise unremarkable, with no evidence of lymphadenopathy. A full examination of the patient's skin including his nails and other mucous membranes was also unremarkable.

What is the most appropriate management of the patient's condition?

[Referral for circumcision14%Skin biopsy20%Referral for patch testing28%Topical ketoconazole gel25%Ultra-potent topical corticosteroid14%](#)

The patient has a presentation consistent with allergic contact dermatitis associated with the glans of his penis. The absence of excessive hygiene routines and principal symptom of itching (rather than burning or pain) make allergic contact dermatitis more likely than irritant dermatitis. The exact causative allergen is unclear from the patient's history, although an ingredient of the toiletries or moisturiser used by the patient (for example, quaternium-15) or latex condoms are possibilities. To define the exact allergen causing the patient's symptoms, he should be referred for formal patch testing.

Topical ketoconazole gel is a possible treatment for genital seborrhoeic dermatitis. Ultra-potent topical corticosteroids are used with caution in the treatment of lichen sclerosis. Skin biopsies are sometimes required in the assessment of male genital dermatoses; for example to exclude epithelial neoplasia in an individual presenting with Zoon's balanitis. Circumcision protects men from inflammatory genital dermatoses - for example, psoriasis, lichen planus and lichen sclerosis - but would not be an appropriate management option in this case.

Shim T, Ali I, Muneer A, Bunker C. Benign male genital dermatoses. BMJ 2016;354:i4337.

## Contact dermatitis

There are two main types of contact dermatitis

- irritant contact dermatitis: common - non-allergic reaction due to weak acids or alkalis (e.g. detergents). Often seen on the hands. Erythema is typical, crusting and vesicles are rare
- allergic contact dermatitis: type IV hypersensitivity reaction. Uncommon - often seen on the head following hair dyes. Presents as an acute weeping eczema which predominately affects the margins of the hairline rather than the hairy scalp itself. Topical treatment with a potent steroid is indicated

Cement is a frequent cause of contact dermatitis. The alkaline nature of cement may cause an irritant contact dermatitis whilst the dichromates in cement also can cause an allergic contact dermatitis

Question 17 of 26

A 17-year-old male presents with a new skin condition which his mum noticed when they were on holiday in Spain. On examination, he has skin type V, with multiple small patches of depigmentation to the upper back. The patches appear mildly flaky but they are asymptomatic. He is usually well and has never had this condition before. Which of the following is the most likely diagnosis?

[Pityriasis rosea 1% Atopic eczema 4% Vitiligo 10% Guttate psoriasis 5% Pityriasis versicolor 69%](#)

This is a typical history of pityriasis versicolor, a skin condition caused by an overgrowth of *Malassezia* yeast. It is most common in young people, especially males. It causes multiple patches of skin discoloration, mainly to the trunk. The patches may appear pale brown, pink, or may appear depigmented especially in patients with dark skin. They may also be mildly flaky and itchy. The condition can often present after spending time in sunny, humid environments. It is treated with topical antifungals eg. ketoconazole shampoo.

Source: NICE CKS Pityriasis versicolor  
<http://cks.nice.org.uk/pityriasis-versicolor#!scenario>

## **Pityriasis versicolor**

Pityriasis versicolor, also called tinea versicolor, is a superficial cutaneous fungal infection caused by *Malassezia furfur* (formerly termed *Pityrosporum ovale*)

### Features

- most commonly affects trunk
- patches may be hypopigmented, pink or brown (hence versicolor). May be more noticeable following a suntan
- scale is common
- mild pruritus

### Predisposing factors

- occurs in healthy individuals
- immunosuppression
- malnutrition
- Cushing's

### Management

- topical antifungal. NICE Clinical Knowledge Summaries advise ketoconazole shampoo as this is more cost effective for large areas
- if extensive disease or failure to respond to topical treatment then consider oral itraconazole

### Question 18 of 26

A 30-year-old woman presents with a painful 'rash' on her shins:



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These have been present for the past 2 weeks. There is no past medical history of note although she had a course of penicillin V for a bout of tonsillitis around a month ago. She also takes Cerazette (a progestogen-only pill) for contraception.

A chest x-ray is requested:



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What is the most likely cause of the skin lesions?

[Lymphoma3%](#)[Sarcoidosis35%](#)[Progestogen-only pill17%](#)[Penicillin42%](#)[Tuberculosis4%](#)

The likely diagnosis here is erythema nodosum (EN). The chest x-ray is completely normal making penicillin the likely culprit in precipitating skin lesions.

The combined oral contraceptive pill is linked to EN rather than the progestogen-only pill.

## Erythema nodosum

### Overview

- inflammation of subcutaneous fat
- typically causes tender, erythematous, nodular lesions
- usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs)
- usually resolves within 6 weeks
- lesions heal without scarring

#### Causes

- infection: streptococci, TB, brucellosis
- systemic disease: sarcoidosis, inflammatory bowel disease, Behcet's
- malignancy/lymphoma
- drugs: penicillins, sulphonamides, combined oral contraceptive pill
- pregnancy



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#### Question 19 of 26

A 54-year-old female presented to the dermatology clinic with a history of worsening itchy rash. She has a history of psoriasis which had been quite well controlled but had worsened significantly in the last week. On examination, there are multiple well-demarcated oval, red/pink elevated lesions with overlying silvery scales over her elbows, knees, legs and scalp. She revealed that her GP had started her on a new tablet 2 weeks ago. Which of the following drugs is likely to have resulted in the above presentation?

[Citalopram11%](#) [Lithium61%](#) [Omeprazole13%](#) [Ranitidine4%](#) [Cimetidine10%](#)

Psoriasis can be exacerbated by certain drugs such as:

- lithium
- beta blockers
- antimalarials



- non-steroidal anti-inflammatory drugs
- ACE-inhibitors
- antibiotics such as tetracycline and penicillin

Withdrawal of systemic steroids can also exacerbate psoriasis.

### **Psoriasis: exacerbating factors**

The following factors may exacerbate psoriasis:

- trauma
- alcohol
- drugs: beta blockers, lithium, antimalarials (chloroquine and hydroxychloroquine), NSAIDs and ACE inhibitors, infliximab
- withdrawal of systemic steroids

Streptococcal infection may trigger guttate psoriasis.

Question 4 of 6

A 55-year-old man develops a rash two days after starting a new medication. The rash is mildly pruritic and mainly affects the arms, torso and neck. The palms of his hand are shown below:



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Which one of the following drugs is most likely to have been started?

[Levetiracetam 10%](#) [Olanzapine 8%](#) [Carbamazepine 70%](#) [Fluoxetine 8%](#) [Diazepam 4%](#)

This patient has developed erythema multiforme which is a known complication of carbamazepine use.

## Erythema multiforme

Erythema multiforme is a hypersensitivity reaction which is most commonly triggered by infections. It may be divided into minor and major forms.

Previously it was thought that Stevens-Johnson syndrome (SJS) was a severe form of erythema multiforme. They are now however considered as separate entities.

### Features

- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild

## Causes

- viruses: herpes simplex virus (the most common cause), Orf\*
- idiopathic
- bacteria: *Mycoplasma*, *Streptococcus*
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus
- sarcoidosis
- malignancy



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### **Erythema multiforme major**

The more severe form, erythema multiforme major is associated with mucosal involvement.



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Example of mucosal involvement in erythema multiforme major

\*Orf is a skin disease of sheep and goats caused by a parapox virus

#### Question 5 of 6

A 60-year-old man with a history of renal transplant presents to the dermatology clinic.

He has a 7mm scaly nodular lesion on his left forearm with an inflamed red base. This appears similar to two squamous cell skin carcinomas he has had excised in the past. The lesion is not painful and he has no lymphadenopathy.

He continues to take tacrolimus, though his dose was lowered following his last squamous cell carcinoma excision. He also suffers from hypertension which is well controlled on ramipril.

His blood tests are as follows:

Hb	120 g/l	Na <sup>+</sup>	136 mmol/l
Platelets	308 * 10 <sup>9</sup> /l	K <sup>+</sup>	4.9 mmol/l
WBC	6 * 10 <sup>9</sup> /l	Urea	5 mmol/l
Neuts	4 * 10 <sup>9</sup> /l	Creatinine	98 µmol/l

What is the most appropriate management?

[Curettage and acitretin19%](#)[Radiotherapy and acitretin8%](#)[Surgery alone27%](#)[Surgery and acitretin42%](#)[Systemic chemotherapy4%](#)

This man has a high risk squamous cell carcinoma (SCC) of the skin given that he is on immunosuppression. He also has a history of previous SCC. Given these factors, surgery is indicated and systemic retinoids, such as acitretin, should be considered to prevent further SCCs.

Curettage is acceptable management for a low risk SCCs. Radiotherapy would be considered post-operatively if there were inadequate tumour margins or evidence of invasion at surgery but is not an appropriate a primary curative therapy in this case. Studies to date have not shown sufficient evidence for systemic chemotherapy for SCC.

In patients on immunosuppression with recurrent SCC, reduction of immunosuppression should be considered and discussion at a multidisciplinary team meeting is warranted.

Reference: Scottish Intercollegiate Guidelines Network. 2014. SIGN 140. Management of primary cutaneous squamous cell carcinoma.

## **Squamous cell carcinoma of the skin**

Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

Risk factors include:

- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

## **Image gallery**





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## **Treatment**

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

## **Prognosis**

### **Good Prognosis**

Well differentiated tumours

<20mm diameter

<2mm deep

No associated diseases

### **Poor prognosis**

Poorly differentiated tumours

>20mm in diameter

>4mm deep

Immunosuppression for whatever reason

#### Question 6 of 6

A 32-year-old man attends his GP with pruritus of the genital area. Additionally, he reports painful intercourse with his long-term partner. Examination reveals a whitish scarred meatus with a white plaque on phimotic foreskin.

What is the most likely diagnosis?

[Candidiasis17%](#) [Vitiligo4%](#) [Lichen planus19%](#) [Lichen sclerosus48%](#) [Erythroplasia of Queyrat11%](#)

Candidiasis will typically cause erythema on the meatus and discharge.

Vitiligo would not be expected to cause painful intercourse or result in phimosis.

Penile lichen planus usually presents with purple papules in a ring around the glans.

Comparatively, lichen sclerosus usually affects the glans and foreskin, resulting in white papules or plaques. It can cause phimosis.

Erythroplasia of Queyrat, also known as an in-situ squamous cell carcinoma of the penis, is a penile intraepithelial neoplasia. It typically occurs in men above 50 years of age, with symptoms including erythema, pain, bleeding and ulcers.

### **Lichen sclerosus**

Lichen sclerosus was previously termed lichen sclerosus et atrophicus. It is an inflammatory condition which usually affects the genitalia and is more common in elderly females. Lichen sclerosus leads to atrophy of the epidermis with white plaques forming

#### Features

- itch is prominent

The diagnosis is usually made on clinical grounds but a biopsy may be performed if atypical features are present\*

#### Management

- topical steroids and emollients

#### Follow-up:

- increased risk of vulval cancer

\*the RCOG advise the following

*Skin biopsy is not necessary when a diagnosis can be made on clinical examination. Biopsy is required if the woman fails to respond to treatment or there is clinical suspicion of VIN or cancer.*

and the British Association of Dermatologists state the following:

*A confirmatory biopsy, although ideal, is not always practical, particularly in children. It is not always essential when the clinical features are typical. However, histological examination is advisable if there are atypical features or diagnostic uncertainty and is mandatory if there is any suspicion of neoplastic change. Patients under routine follow-up will need a biopsy if:*

- (i) *there is a suspicion of neoplastic change, i.e. a persistent area of hyperkeratosis, erosion or erythema, or new warty or papular lesions;*
- (ii) *the disease fails to respond to adequate treatment;*
- (iii) *there is extragenital LS, with features suggesting an overlap with morphoea;*
- (iv) *there are pigmented areas, in order to exclude an abnormal melanocytic proliferation;*

*and*

- (v) *second-line therapy is to be used.*